EXHIBIT 4

UNITED STATES PATENT AND TRADEMARK OFFICE 12006.64SRX

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/007,913	02/01/2006	6284478	518852800200	5776

23552 7590 02/24/2006

MERCHANT & GOULD PC MD
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED: 02/24/2006

Owners Statement
Apr 24, 2006
DV

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

DO NOT USE IN PALM PRINTER

(THIRD PARTY REQUESTER'S CORRESPONDENCE ADDRESS)

Peng Chen

MORRISON & FORESTER LLP

12531 HIGH BLUFF DRIVE, SUITE 100

SAN DIEGO, CA 92130

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/007,913*.

PATENT NO. *6284478*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Order Granting / Denying Request For Ex Parte Reexamination	Control No.	Patent Under Reexamination	
	90/007,913	6284478	
	Examiner	Art Unit	
	Evelyn Huang	3991	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed *01 February 2006* has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)☒ PTO-892, b)☐ PTO-1449, c)☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

a) ☐ by Treasury check or,

b) ☐ by credit to Deposit Account No. _____, or

c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

Evelyn Huang
Primary Examiner
Art Unit: 3991

cc:Requester (if third party requester)

Notice of References Cited	Application/Control No. 90/007,913	Applicant(s)/Patent Under Reexamination 6284478	
	Examiner Evelyn Huang	Art Unit 3991	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,986,271	01-1991	Wilkins, Ebtisam S.	600/347
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
*	U	Sakakida et al. Sensors and Actuators B, 13-14: 319-322 (May-June, 1993).
*	V	Sternberg et al. Biosensors, 4:27-40 (1988).
*	W	Sakakida et al. (II). Artif. Organs Today, 2(2) :145-158 (1992).
*	X	Shichiri et al. Diab. Nutr. Metab., 2:309-313 (1989).

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Reexamination

Decision Granting Ex Parte Reexamination

1. A substantial new question of patentability affecting claims 1-74 of United States Patent Number 6,284,478 to Heller is raised by the request for *ex parte* reexamination.

Procedural Posture

2. The request by the Third Party Requester for *ex parte* reexamination is filed on 2/1/2006.

Ongoing Duty to Disclose

3. A PTO-1449 has not been filed with the references submitted by the Third Party Requester. The submitted references considered by the examiner are cited in a PTO-892.

4. The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a) to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 6,284,478 throughout the course of this reexamination proceeding. The third party requester is also reminded of the ability to similarly apprise the Office of any such activity or proceeding throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

Priority

4. US 6,284,478, the patent under reexamination, is a continuation of US Application No. 08/299,526, filed on 9-1-1994, issued as US Patent No. 5,593,853, which is a CIP of US Application No. 08/161,682, filed on 12-2-1993, issued as US Patent No. 5,356,786, which is a continuation of US Application No. 07/664,054, filed on 3-4-1991, now abandoned.

5. US Application No. 08/161,682, filed on 12-2-1993, issued as US Patent No. 5,356,786, only describes a glucose electrode coated with an oxidizing enzyme (peroxidase) which allows hydrogen peroxide to selectively oxidize the interferants (as described in Fig. 6). The electrode of the instant invention having preferably three or four layers, including the interference eliminating layer (as described in Fig. 1), was first described in US Application No. 08/299,526, filed on 9-1-1994, issued as US Patent No. 5,593,853. Accordingly, the earliest effective filing date for the patent claims under reexamination is 9-1-1994.

References Cited by the Third Party Requester

6. ***Old References***

Wilkins US 4,986,271

Sakakida et al. (I) Sensors and Actuators B, 13-14: 319-322 (May-June, 1993).

Sternberg et al. Biosensors, 4:27-40 (1988).

7. ***New References***

Sakakida et al. (II). Artif. Organs Today, 2(2) :145-158 (1992).

Shichiri et al. Diab. Nutr. Metab., 2:309-313 (1989).

Claims in U.S. 6,284,478

8. Claims 1-3 are directed to an electrochemical sensor comprising (a) one or more non-corroding metal or carbon electrodes; (b) a sensing layer comprising an enzyme coupled to each electrode; and (c) a biocompatible layer comprising a biocompatible hydrogel chemically bound to the sensing layer of each electrode.

Claim 4 is directed to an analyte measurement system comprising (a) an electrochemical sensor including two or more non-corroding metal or carbon electrodes, each electrode adapted for subcutaneous implantation in animal, and a non-leachable analyte-responsive enzyme disposed on each of the electrodes; and (b) a device for comparing signals of the two electrodes.

Claims 5-8 are directed an electrochemical sensor comprising (a) one or more non-corroding metal or carbon electrodes; (b) a sensing layer coupled to each electrode wherein the sensing layer comprises a non-leachable redox enzyme; and (c) a microfiltration device for transporting a fluid sample into contact with the sensing layer of at least one of the electrodes.

Claims 9-51, 74 are directed to an electrochemical sensor for measuring an analyte in an animal, comprising one or more analyte responsive electrodes, at lease one electrode adapted for subcutaneous implantation in animal, each of the analyte responsive electrode comprises (a) one two or more non-corroding metal or carbon electrodes and a non-leachable analyte-responsive

enzyme disposed on each of the electrodes; and (b) a sensing layer comprising a redox enzyme and a redox compound, which are non-leachable fluids in the body of the animal at a pH of 6.5-7.8.

Claims 52-63, 70-73 are directed to a method of calibrating an electrochemical sensor comprising (a) withdrawing a single calibration sample from an animal; (b) assaying an analyte concentration of the sample; and (c) correlating the assayed analyte concentration to a signal generated by one or more implanted working electrode having an analyte-responsive enzyme disposed thereon.

Claims 64-69 are directed to a method for the analysis of a bioanalyte comprising (a) providing an analyte measurement system comprising two or more subcutaneously implantable electrodes; (b) subcutaneously implanting 2 or more electrodes in the animal; (c) obtaining readings from the electrodes at substantially one point in time; (d) comparing two or more of the readings of the electrodes; and (e) accepting those readings which do not vary by more than a predetermined degree.

Substantial New Question of Patentability

9. *For "a substantial new question of patentability" to be present, it is only necessary that:*

A. The prior art patents and/or printed publications raise a substantial question of patentability regarding at least one claim, i.e., the teaching of the (prior art) patents and printed publications is such that a reasonable examiner would consider the teaching to be

important in deciding whether or not the claim is patentable; it is not necessary that the prior art establish a prima facie case of unpatentability; and

B. The same question of patentability as to the claim has not been decided by the Office in a previous examination or pending reexamination of the patent or in a final holding of invalidity by the Federal Courts in a decision on the merits involving the claim.

For any reexamination ordered on or after November 2, 2002, reliance on previously cited/considered art, i.e., "old art," does not necessarily preclude the existence of a substantial new question of patentability (SNQ) that is based exclusively on that old art. Rather, determinations on whether a SNQ exists in such an instance shall be based upon a fact-specific inquiry done on a case-by-case basis. See MPEP 2242.

If a substantial new question of patentability is found as to one claim, all claims will be reexamined during the ex parte reexamination process. See MPEP 2216.

Discussion of the Cited references

10. ***Sakakida I*** raises a substantial new question of patentability as to claims 1-74 of the Heller patent.

Sakakida discloses a ferrocene-mediated needle-type glucose sensor wherein glucose oxidase (redox enzyme) and ferrocene carboxaldehyde (redox compound) were immobilized to cellulose diacetate (a polymer) on the platinum electrode. The surface of the sensor was covered with a glucose flux-limiting hydrophobic polyurethane membrane and a biocompatible hydrophilic polyvinyl alcohol membrane (page 319, Materials and Methods; page 320, Fig. 1). The oxygen tension does not affect the output current in the ferrocene-mediated glucose sensor (page 321, 3.1). Furthermore, it requires only one point in situ calibration (page 319, abstract).

There is a substantial likelihood that a reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable. This reference was cited, but was not applied, during the prosecution of the application which became the Heller patent. It is now being viewed in a new light or in different ways. Accordingly, this reference raises a substantial new question of patentability as to claims 1-74, which question has not been decided in a previous examination of the Heller patent.

11. ***Sternberg*** raises a substantial new question of patentability as to claims 1-74 of the Heller patent.

Sternberg discloses a multilayer needle-type enzyme-based glucose microsensor. More specifically, glucose oxidase (redox enzyme) covalently coupled to a cellulose acetate layer, using bovine serum albumin and parabenzoquinone (redox compound) is deposited on the platinum electrode. The sensor is covered with an outer layer of polyurethane (page 27, abstract; page 29, Fig. 1).

There is a substantial likelihood that a reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable. This reference was cited, but was not applied, during the prosecution of the application which became the Heller patent. It is now being viewed in a new light or in different ways. Accordingly, this reference raises a substantial new question of patentability as to claims 1-74, which question has not been decided in a previous examination of the Heller patent.

12. ***Schichiri*** together with Sakakida (paragraph 10 above) raise a substantial new question of patentability as to claims 1-74 of the Heller patent.

Schichiri teaches that polyethylene oxide (PEO) membrane is a biocompatible membrane comparable to polyvinyl alcohol membrane. PEO membrane has the in vivo characteristics that its strength of membrane is excellent and the sensor output is good (page 312, Table 2).

There is a substantial likelihood that a reasonable examiner would consider Schichiri's teaching together with the teaching of Sakakida important in deciding whether or not the claims are patentable. Schichiri was not cited during the prosecution of the application which became the Heller patent. Accordingly, Schichiri together with Sakakida raise a substantial new question of patentability as to claims 1-74, which question has not been decided in a previous examination of the Heller patent.

13. ***Wilkins (US 4,986,271)*** raises a substantial new question of patentability as to claims 1-74 of the Heller patent.

Wilkins discloses an refillable implantable glucose sensor (Fig. 1) wherein the sensing layer comprises glucose oxidase covalently cross linked to the modified graphite (column 4, Example 1) or an electrically conducting polymer (column 4, lines 1-4). The sensing layer is in contact with the working metal electrode (column 3, line 50).

There is a substantial likelihood that a reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable. This reference was cited, but was not applied during the prosecution of the application which became the Heller patent. It is now being viewed in a new light or in different ways. Accordingly, this reference raises a substantial

new question of patentability as to claims 1-74, which question has not been decided in a previous examination of the Heller patent.

14. ***Sakakida II*** discloses a ferrocene-mediated needle-type glucose sensor wherein glucose oxidase (redox enzyme) and ferrocene carboxaldehyde (redox compound) were immobilized to cellulose diacetate (a polymer) on the platinum electrode. The surface of the sensor was covered with a glucose flux-limiting hydrophobic polyurethane membrane and a biocompatible hydrophilic polyvinyl alcohol membrane (page 147, Fig 1).

There is a substantial likelihood that a reasonable examiner would consider this teaching important in deciding whether or not the claims are patentable. This reference was not cited during the prosecution of the application which became the Heller patent. Accordingly, this reference raises a substantial new question of patentability as to claims 1-74, which question has not been decided in a previous examination of the Heller patent.

Extensions of Time

15. Extensions of time under 37 CFR 1.136(a) will not be permitted in these proceedings because the provisions of 37 CFR 1.136 apply only to "an applicant" and not to parties in a reexamination proceeding. Additionally, 35 U.S.C. 305 requires that *ex parte* reexamination proceedings "will be conducted with special dispatch" (37 CFR 1.550(a)). Extensions of time in *ex parte* reexamination proceedings are provided for in 37 CFR 1.550(c).

Future Amendment

16. Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37CFR 1.20(c).

Future Correspondence

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By Mail to:	Mail Stop ex parte Reexam Central Reexamination Unit Office of Patent Legal Administration United States Patent & Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450
By FAX to:	571-273-9900 Central Reexamination Unit
By Hand to:	Customer Service Window Randolph Building 401 Dulany St. Alexandria, VA 22314

Evelyn Huang
Primary Examiner
Art Unit 3991

Conferee

EXHIBIT 5

US006175752B1

(12) **United States Patent**
Say et al.

(10) **Patent No.: US 6,175,752 B1**
(45) **Date of Patent: Jan. 16, 2001**

(54) **ANALYTE MONITORING DEVICE AND METHODS OF USE**

(75) Inventors: **James Say**, Alameda; **Michael F. Tomasco**, Cupertino, both of CA (US); **Adam Heller**, Austin, TX (US); **Yoram Gal**, Kibbutz Yagur (IL); **Behrad Aria**, Alameda, CA (US); **Ephraim Heller**, Oakland, CA (US); **Phillip John Plante**, Sunnyvale, CA (US); **Mark S. Vreeke**, Alameda, CA (US); **Keith A. Friedman**, Austin, TX (US); **Fredric C. Colman**, Berkeley, CA (US)

(73) Assignee: **Therasense, Inc.**, Alameda, CA (US)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/070,677**

(22) Filed: **Apr. 30, 1998**

(51) **Int. Cl.**[7] **A61B 5/05**

(52) **U.S. Cl.** **600/345**; 600/365; 128/903

(58) **Field of Search** 600/300–301, 600/346, 306–309, 345–365, 372, 385–390; 604/174–180; 128/897–898, 903, 904, 920

(56) **References Cited**

U.S. PATENT DOCUMENTS

Re. 32,947	6/1989	Dormer et al. .
3,260,656	7/1966	Ross, Jr. .
3,653,841	4/1972	Klein .
3,719,564	3/1973	Lilly, Jr. et al. .
3,776,832	12/1973	Oswin et al. .
3,837,339	9/1974	Aisenberg et al. .
3,926,760	12/1975	Allen et al. .
3,972,320	8/1976	Kalman .
3,979,274	9/1976	Newman .
4,008,717	2/1977	Kowarski .
4,016,866	4/1977	Lawton .
4,055,175	10/1977	Clemens et al. .
4,059,406	11/1977	Fleet .
4,076,596	2/1978	Connery et al. .
4,098,574	7/1978	Dappen .
4,100,048	7/1978	Pompei et al. .

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

227 029 A3	9/1985	(DD) .
29 03 216	8/1979	(DE) .

(List continued on next page.)

OTHER PUBLICATIONS

Abruna, H. D. et al., "Rectifying Interfaces Using Two–Layer, Films of Electrochemically Polymerized Vinylpyridine and Vinylbipyridine Complexes of Ruthenium and Iron on Electrodes," *J. Am. Chem. Soc.*, 103(1):1–5 (Jan. 14, 1981).

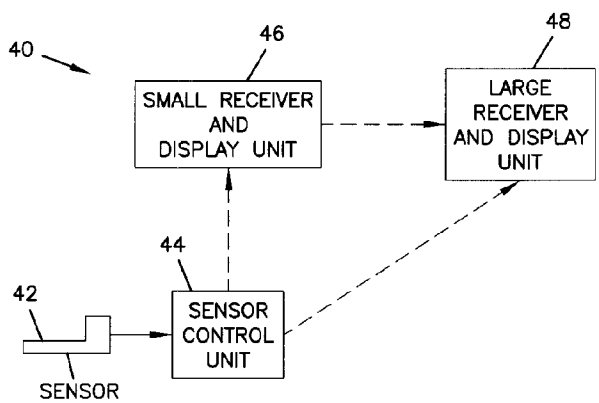
(List continued on next page.)

Primary Examiner—Cary O'Connor
Assistant Examiner—Michael Astorino
(74) *Attorney, Agent, or Firm*—Merchant & Gould P.C.

(57) **ABSTRACT**

An analyte monitor includes a sensor, a sensor control unit, and a display unit. The sensor has, for example, a substrate, a recessed channel formed in the substrate, and conductive material disposed in the recessed channel to form a working electrode. The sensor control unit typically has a housing adapted for placement on skin and is adapted to receive a portion of an electrochemical sensor. The sensor control unit also includes two or more conductive contacts disposed on the housing and configured for coupling to two or more contact pads on the sensor. A transmitter is disposed in the housing and coupled to the plurality of conductive contacts for transmitting data obtained using the sensor. The display unit has a receiver for receiving data transmitted by the transmitter of the sensor control unit and a display coupled to the receiver for displaying an indication of a level of an analyte. The analyte monitor may also be part of a drug delivery system to alter the level of the analyte based on the data obtained using the sensor.

94 Claims, 26 Drawing Sheets



U.S. PATENT DOCUMENTS

4,151,845	5/1979	Clemens .	4,781,798	11/1988	Gough .		
4,168,205	9/1979	Danninger et al. .	4,784,736	11/1988	Lonsdale et al. .		
4,172,770	10/1979	Semersky et al. .	4,795,707	1/1989	Niiyama et al. .		
4,178,916	12/1979	McNamara .	4,796,634	1/1989	Huntsman et al. .		
4,206,755	6/1980	Klein .	4,805,624	2/1989	Yao et al. .		
4,224,125	9/1980	Nakamura et al. .	4,813,424	3/1989	Wilkins .		
4,240,438	12/1980	Updike et al. .	4,815,469	3/1989	Cohen et al. .		
4,247,297	1/1981	Berti et al. .	4,820,399	4/1989	Senda et al. .		
4,340,458	7/1982	Lerner et al. .	4,822,337	4/1989	Newhouse et al. .		
4,352,960	10/1982	Dormer et al. .	4,830,959	5/1989	McNeil et al. .		
4,356,074	10/1982	Johnson .	4,832,797	5/1989	Vadgama et al. .		
4,365,637	12/1982	Johnson .	4,840,893	6/1989	Hill et al. .		
4,366,033	12/1982	Richter et al. .	4,848,351	7/1989	Finch .		
4,375,399	3/1983	Havas et al. .	4,871,351	10/1989	Feingold .		
4,384,586	5/1983	Christiansen .	4,871,440	10/1989	Nagata et al. .		
4,390,621	6/1983	Bauer .	4,874,500	10/1989	Madou et al. .		
4,401,122	8/1983	Clark, Jr. .	4,890,620	1/1990	Gough .		
4,404,066	9/1983	Johnson .	4,894,137	1/1990	Takizawa et al. .		
4,418,148	11/1983	Oberhardt .	4,897,162	1/1990	Lewandowski et al. .		
4,427,770	1/1984	Chen et al. .	4,897,173	1/1990	Nankai et al. .		
4,431,004	2/1984	Bessman et al. .	4,909,908	3/1990	Ross et al. .		
4,436,094	3/1984	Cerami .	4,911,794	3/1990	Parce et al. .		
4,440,175	4/1984	Wilkins .	4,917,800	4/1990	Lonsdale et al. .		
4,450,842	5/1984	Zick et al. .	4,919,141	4/1990	Zier et al. .		
4,458,686	7/1984	Clark, Jr. .	4,919,767	4/1990	Vadgama et al. .		
4,461,691	7/1984	Frank .	4,923,586	5/1990	Katayama et al. .		
4,469,110	9/1984	Slama .	4,927,516	5/1990	Yamaguchi et al. .		
4,477,314	10/1984	Richter et al. .	4,934,369	6/1990	Maxwell .		
4,484,987	11/1984	Gough .	4,935,105	6/1990	Churchouse .		
4,522,690	6/1985	Venkatsetty .	4,935,345	6/1990	Guilbeau et al. .		
4,524,114	6/1985	Samuels et al. .	4,938,860	7/1990	Wogoman .		
4,526,661	7/1985	Steckhan et al. .	4,944,299	7/1990	Silvian .		
4,534,356	8/1985	Papadakis .	4,950,378	8/1990	Nagara .		
4,538,616	9/1985	Rogoff .	4,953,552	* 9/1990	DeMarzo	600/300	
4,543,955	10/1985	Schroeppel .	4,954,129	9/1990	Giuliani et al. .		
4,545,382	10/1985	Higgins et al. .	4,969,468	11/1990	Byers et al. .		
4,552,840	11/1985	Riffer .	4,970,145	11/1990	Bennetto et al. .		
4,560,534	12/1985	Kung et al. .	4,974,929	12/1990	Curry .		
4,571,292	2/1986	Liu et al. .	4,986,271	1/1991	Wilkins .		
4,573,994	3/1986	Fischell et al. .	4,994,167	2/1991	Shults et al. .		
4,581,336	4/1986	Malloy et al. .	5,001,054	3/1991	Wagner .		
4,595,011	6/1986	Phillips .	5,050,612	9/1991	Matsumura .		
4,619,754	10/1986	Niki et al. .	5,058,592	10/1991	Whisler .		
4,627,445	12/1986	Garcia et al. .	5,070,535	12/1991	Hochmair et al. .		
4,627,908	12/1986	Miller .	5,082,550	1/1992	Rishpon et al. .		
4,633,878	1/1987	Bombardieri .	5,082,786	1/1992	Nakamoto .		
4,637,403	1/1987	Garcia et al. .	5,089,112	2/1992	Skotheim et al. .		
4,650,547	3/1987	Gough .	5,095,904	3/1992	Seligman et al. .		
4,654,197	3/1987	Lilja et al. .	5,101,814	4/1992	Palti .		
4,655,880	4/1987	Liu .	5,108,564	4/1992	Szuminsky et al. .		
4,655,885	4/1987	Hill et al. .	5,109,850	5/1992	Blanco et al. .		
4,671,288	6/1987	Gough .	5,120,420	6/1992	Nankai et al. .		
4,679,562	7/1987	Luksha .	5,126,034	6/1992	Carter et al. .		
4,680,268	7/1987	Clark, Jr. .	5,133,856	7/1992	Yamaguchi et al. .		
4,682,602	7/1987	Prohaska .	5,135,003	8/1992	Souma .		
4,684,537	8/1987	Graetzel et al. .	5,141,868	8/1992	Shanks et al. .		
4,685,463	8/1987	Williams .	5,161,532	11/1992	Joseph .		
4,703,756	11/1987	Gough et al. .	5,165,407	11/1992	Wilson et al. .		
4,711,245	12/1987	Higgins et al. .	5,174,291	12/1992	Schoonen et al. .		
4,717,673	1/1988	Wrighton et al. .	5,190,041	3/1993	Palti .		
4,721,601	1/1988	Wrighton et al. .	5,192,416	3/1993	Wang et al. .		
4,721,677	1/1988	Clark, Jr. .	5,198,367	3/1993	Aizawa et al. .		
4,726,378	2/1988	Kaplan .	5,202,261	4/1993	Musho et al. .		
4,726,716	2/1988	McGuire .	5,205,920	4/1993	Oyama et al. .		
4,757,022	7/1988	Shults et al. .	5,208,154	5/1993	Weaver et al. .		
4,758,323	7/1988	Davis et al. .	5,209,229	5/1993	Gilli .		
4,759,371	7/1988	Franetzki .	5,217,595	6/1993	Smith et al. .		
4,759,828	7/1988	Young et al. .	5,229,282	7/1993	Yoshioka et al. .		
4,764,416	8/1988	Ueyama et al. .	5,250,439	10/1993	Musho et al. .		
4,776,944	10/1988	Janata et al. .	5,262,035	11/1993	Gregg et al. .		
			5,262,305	11/1993	Heller et al. .		

5,264,103		11/1993	Yoshioka et al. .	
5,264,104		11/1993	Gregg et al. .	
5,264,106		11/1993	McAleer et al. .	
5,271,815		12/1993	Wong .	
5,279,294		1/1994	Anderson et al. .	
5,286,362		2/1994	Hoenes et al. .	
5,286,364		2/1994	Yacynych et al. .	
5,288,636		2/1994	Pollmann et al. .	
5,293,546		3/1994	Tadros et al. .	
5,320,098		6/1994	Davidson .	
5,320,725		6/1994	Gregg et al. .	
5,322,063	*	6/1994	Allen et al.	600/372
5,337,747		8/1994	Neftel .	
5,352,348		10/1994	Young et al. .	
5,356,348		10/1994	Young et al. .	
5,356,786		10/1994	Heller et al. .	
5,368,028		11/1994	Palti .	
5,372,133		12/1994	Hogen Esch .	
5,376,251		12/1994	Kaneko et al. .	
5,378,628		1/1995	Gratzel et al. .	
5,387,327		2/1995	Khan .	
5,390,671		2/1995	Lord et al. .	
5,391,250		2/1995	Cheney, II et al. .	
5,395,504		3/1995	Saurer et al. .	
5,400,782	*	3/1995	Beaubiah	600/309
5,411,647		5/1995	Johnson et al. .	
5,437,999		8/1995	Diebold et al. .	
5,469,846		11/1995	Khan .	
5,491,474	*	2/1996	Suni et al.	128/903
5,494,562		2/1996	Maley et al. .	
5,496,453		3/1996	Uenoyama et al. .	
5,497,772		3/1996	Schulman et al. .	
5,531,878		7/1996	Vadgama et al. .	
5,545,191		8/1996	Mann et al. .	
5,560,357		10/1996	Faupel et al. .	
5,562,713	*	10/1996	Silvian	128/903
5,565,085		10/1996	Ikeda et al. .	
5,567,302		10/1996	Song et al. .	
5,568,806		10/1996	Cheney, II et al. .	
5,569,186		10/1996	Lord et al. .	
5,582,184		12/1996	Erickson et al. .	
5,582,697		12/1996	Ikeda et al. .	
5,582,698		12/1996	Flaherty et al. .	
5,586,553		12/1996	Halili et al. .	
5,589,326		12/1996	Deng et al. .	
5,593,852		1/1997	Heller et al. .	
5,596,150		1/1997	Arndt et al. .	
5,617,851		4/1997	Lipkovker .	
5,628,890		5/1997	Carter et al. .	
5,651,869		7/1997	Yoshioka et al. .	
5,660,163		8/1997	Schulman et al. .	
5,670,031		9/1997	Hintsche et al. .	
5,680,858		10/1997	Hansen et al. .	
5,682,233		10/1997	Brinda .	
5,695,623		12/1997	Michel et al. .	
5,708,247		1/1998	McAleer et al. .	
5,711,297	*	1/1998	Iliff et al.	600/300
5,711,861	*	1/1998	Ward et al.	600/365
5,711,862		1/1998	Sakoda et al. .	
5,741,211		4/1998	Renirie et al. .	
5,771,001	*	6/1998	Cobb	128/903
5,791,344	*	8/1998	Schulman et al.	600/300
5,800,420	*	9/1998	Gross et al.	604/890.1
5,807,375		9/1998	Gross et al. .	
5,820,551	*	10/1998	Hill et al.	600/365
5,820,622	*	10/1998	Gross et al.	604/890.1
5,822,715		10/1998	Worthington et al. .	
5,827,184	*	10/1998	Netherly et al.	600/385
5,840,020		11/1998	Heinonen et al. .	
5,842,983	*	12/1998	Abel et al.	600/372
5,885,211	*	3/1999	Eppstein et al.	600/365
5,954,685	*	9/1999	Tierny	600/386
5,971,922	*	10/1999	Arita et al.	600/365

FOREIGN PATENT DOCUMENTS

3934299	10/1990	(DE) .
0 010 375 A1	4/1980	(EP) .
0 026 995 A1	4/1981	(EP) .
0 048 090 A2	3/1982	(EP) .
0 078 636 A1	5/1983	(EP) .
0 096 228 A1	12/1983	(EP) .
0 125 139 A2	11/1984	(EP) .
0 127 958 A2	12/1984	(EP) .
0 136 362 A1	4/1985	(EP) .
0 170 375 A2	2/1986	(EP) .
0 177 743 A2	4/1986	(EP) .
0 080 304 B1	5/1986	(EP) .
0 184 909 A2	6/1986	(EP) .
0 206 218 A2	12/1986	(EP) .
0 230 472 A1	8/1987	(EP) .
0 241 309 A3	10/1987	(EP) .
0 245 073 A2	11/1987	(EP) .
0 278 647 A2	8/1988	(EP) .
0 359 831 A1	3/1990	(EP) .
0 368 290 A1	10/1990	(EP) .
390 390 A1	10/1990	(EP) .
0 400 918 A1	12/1990	(EP) .
0 453 283 A1	10/1991	(EP) .
0 470 290 A1	2/1992	(EP) .
0 127 958 B2	3/1992	(EP) .
0 255 291 B1	6/1992	(EP) .
1394171	5/1975	(GB) .
1599241	9/1981	(GB) .
2 073 891	10/1981	(GB) .
2 154 003	2/1988	(GB) .
2 204 408	11/1988	(GB) .
2 254 436	10/1992	(GB) .
54-41191	4/1979	(JP) .
55-10581	1/1980	(JP) .
55-10583	1/1980	(JP) .
55-10584	1/1980	(JP) .
55-12406	1/1980	(JP) .
56-163447	12/1981	(JP) .
57-70448	4/1982	(JP) .
60-173457	9/1985	(JP) .
60-173458	9/1985	(JP) .
60-173459	9/1985	(JP) .
61-90050	5/1986	(JP) .
62-85855	4/1987	(JP) .
62-114747	5/1987	(JP) .
63-58149	3/1988	(JP) .
63-128252	5/1988	(JP) .
63-139246	6/1988	(JP) .
63-294799	12/1988	(JP) .
63-317757	12/1988	(JP) .
63-317758	12/1988	(JP) .
1-114746	5/1989	(JP) .
1-114747	5/1989	(JP) .
1-124060	5/1989	(JP) .
1-134244	5/1989	(JP) .
1-156658	6/1989	(JP) .
2-62958	3/1990	(JP) .
2-120655	5/1990	(JP) .
2-287145	11/1990	(JP) .
2-310457	12/1990	(JP) .
3-26956	2/1991	(JP) .
3-28752	2/1991	(JP) .
3-202764	9/1991	(JP) .
5-72171	3/1993	(JP) .
5-196595	8/1993	(JP) .
6-190050	7/1994	(JP) .
7-55757	3/1995	(JP) .

7-72585	3/1995	(JP) .
8-285814	11/1996	(JP) .
8-285815	11/1996	(JP) .
9-21778	1/1997	(JP) .
9-101280	4/1997	(JP) .
9-285459	11/1997	(JP) .
10-170471	6/1998	(JP) .
1281988 A1	1/1987	(SU) .
WO 89/05119	11/1985	(WO) .
WO 89/08713	9/1989	(WO) .
WO 90/05300	5/1990	(WO) .
WO 90/05910	5/1990	(WO) .
WO 91/01680	2/1991	(WO) .
WO 91/04704	4/1991	(WO) .
WO 91/15993	10/1991	(WO) .
WO 92/13271	8/1992	(WO) .
WO 94/20602	9/1994	(WO) .
WO 94/27140	11/1994	(WO) .
WO 96/30431	10/1996	(WO) .
WO 96/35370	11/1996	(WO) .
WO 97/02847	1/1997	(WO) .
WO 97/19344	5/1997	(WO) .
WO 97/42882	11/1997	(WO) .
WO 97/42883	11/1997	(WO) .
WO 97/42886	11/1997	(WO) .
WO 97/42888	11/1997	(WO) .
WO 97/43962	11/1997	(WO) .

OTHER PUBLICATIONS

Albery, W. J. et al., "Amperometric enzyme electrodes. Part II. Conducting salts as electrode materials for the oxidation of glucose oxidase," *J. Electroanal. Chem. Interfacial Electrochem.,* 194(2) (1 page—Abstract only) (1985).

Albery, W. J. et al., "Amperometric Enzyme Electrodes," *Phil. Trans. R Soc. Lond.* B316:107–119 (1987).

Alcock, S. J. et al., "Continuous Analyte Monitoring to Aid Clinical Practice," *IEEE Engineering in Medicine and Biology,* 319–325 (1994).

Anderson, L. B. et al., "Thin–Layer Electrochemistry: Steady–State Methods of Studying Rate Processes," *J. Electroanal. Chem.,* 10:295–395 (1965).

Bartlett, P. N. et al., "Covalent Binding of Electron Relays to Glucose Oxidation," *J. Chem. Soc. Chem. Commun.,* 1603–1604 (1987).

Bartlett, P. N. et al., "Modification of glucose oxidase by tetrathiafulvalene," *J. Chem. Soc., Chem. Commun.,* 16 (1 page—Abstract only) (1990).

Bartlett, P. N. et al., "Strategies for the Development of Amperometric Enzyme Electrodes," *Biosensors,* 3:359–379 (1987/88).

Bindra, D.S. et al., "Design and in Vitro Studies of a Needle–Type Glucose Sensor for Subcutaneous Monitoring", *Anal. Chem.,* 63(17):1692–1696 (Sep. 1, 1991).

Bobbioni–Harsch, E. et al., "Lifespan of subcutaneous glucose sensors and their performances during dynamic glycaemia changes in rats," *J. Biomed. Eng.* 15:457–463 (1993).

Brandt J. et al., "Covalent attachment of proteins to polysaccharide carriers by means of benzoquinone," *Biochim. Biophys. Acta,* 386(1) (1 page Abstract only) (1975).

Brownlee, M. et al., "A Glucose–Controlled Insulin–Delivery System: Semisynthetic Insulin Bound to Lectin", *Science,* 206(4423):1190–1191 (Dec. 7, 1979).

Cass, A.E.G. et al., "Ferricinum Ion As An Electron Acceptor for Oxido–Reductases," *J. Electroanal. Chem.,* 190:117–127 (1985).

Cass, A.E.G. et al., "Ferrocene–Mediated Enzyme Electrode for Amperometric Determination of Glucose", *Anal. Chem.,* 56(4):667–671 (Apr. 1984).

Castner, J. F. et al., "Mass Transport and Reaction Kinetic Parameters Determined Electrochemically for Immobilized Glucose Oxidase," *Biochemistry,* 23(10):2203–2210 (1984).

Claremont, D.J. et al., "Biosensors for Continuous In Vivo Glucose Monitoring", *IEEE Engineering in Medicine and Biology Society 10th Annual International Conference,* New Orleans, Louisiana, 3 pgs. (Nov. 4–7, 1988).

Clark L.C. et al., "Differential Anodic Enzyme Polarography for the Measurement of Glucose", *Oxygen Transport to Tissue: Instrumentation, Methods, and Physiology,* 127–132 (1973).

Clark, L.C., Jr. et al., "Electrode Systems for Continuous Monitoring in Cardiovascular Surgery," *Annals New York Academy of Sciences,* pp. 29–45 (1962).

Clark, L.C. et al., "Long–term Stability of Electroenzymatic Glucose Sensors Implanted in Mice," *Trans. Am. Soc. Artif. Intern. Organs,* XXXIV:259–265 (1988).

Clarke, W. L., et al., "Evaluating Clinical Accuracy of Systems for Self–Monitoring of Blood Glucose," *Diabetes Care,* 10(5):622–628 (Sep.–Oct. 1987).

Csöregi, E. et al., "Design, Characterization, and One–Point in Vivo Calibration of a Subcutaneously Implanted Glucose Electrode," *Anal. Chem.* 66(19):3131–3138 (Oct. 1, 1994).

Csöregi, E. et al., "Design and Optimization of a Selective Subcutaneously Implantable Glucose Electrode Based on "Wired" Glucose Oxidase," *Anal. Chem.* 67(7):1240–1244 (Apr. 1, 1995).

Csöregi, E. et al., "On–Line Glucose Monitoring by Using Microdialysis Sampling and Amperometric Detection Based on "Wired" Glucose Oxidase in Carbon Paste," *Mikrochim. Acta.* 121:31–40 (1995).

Davis, G., "Electrochemical Techniques for the Development of Amperometric Biosensors", *Biosensors,* 1:161–178 (1985).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 1. Electron Transfer from Glucose Oxidase to Metal Electrodes via Electron Relays, Bound Covalently to the Enzyme," *J. Phys. Chem.* 91(6):1285–1289 (1987).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 2. Methods for Bonding Electron–Transfer Relays to Glucose Oxidase and D–Amino–Acid Oxidase," *J. Am. Chem. Soc.,* 110(8):2615–2620 (1988).

Degani, Y. et al., "Electrical Communication between Redox Centers of Glucose Oxidase and Electrodes via Electrostatically and Covalently Bound Redox Polymers," *J. Am. Chem. Soc.,* 111:2357–2358 (1989).

Denisevich, P. et al., "Unidirectional Current Flow and Charge State Trapping at Redox Polymer Interfaces on Bilayer Electrodes: Principles, Experimental Demonstration, and Theory," *J. Am. Chem. Soc.,* 103(16):4727–4737 (1981).

Dicks, J. M., "Ferrocene modified polypyrrole with immobilised glucose oxidase and its application in amperometric glucose microbiosensors," *Ann. Biol. clin.,* 47:607–619 (1989).

Engstrom, R.C., "Electrochemical Pretreatment of Glassy Carbon Electrodes", *Anal. Chem.,* 54(13):2310–2314 (Nov. 1982).

Engstrom, R.C. et al., "Characterization of Electrochemically Pretreated Glassy Carbon Electrodes", *Anal. Chem.,* 56(2):136–141 (Feb. 1984).

Ellis, C. D., "Selectivity and Directed Charge Transfer through an Electroactive Metallopolymer Film," *J. Am. Chem. Soc.,* 103(25):7480–7483 (1981).

Feldman, B.J. et al., "Electron Transfer Kinetics at Redox Polymer/Solution Interfaces Using Microelectrodes and Twin Electrode Thin Layer Cells", *J. Electroanal. Chem.,* 194(1):63–81 (Oct. 10, 1985).

Fischer, H. et al., "Intramolecular Electron Transfer Mediated by 4,4'–Bipyridine and Related Bridging Groups", *J. Am. Chem. Soc.,* 98(18):5512–5517 (Sep. 1, 1976).

Foulds, N.C. et al., "Enzyme Entrapment in Electrically Conducting Polymers," *J. Chem. Soc., Faraday Trans 1.,* 82:1259–1264 (1986).

Foulds, N.C. et al., "Immobilization of Glucose Oxidase in Ferrocene–Modified Pyrrole Polymers," *Anal. Chem.,* 60(22):2473–2478 (Nov. 15, 1988).

Frew, J.E. et al., "Electron–Transfer Biosensors", *Phil. Trans. R Soc. Lond.,* B316:95–106 (1987).

Gorton, L. et al., "Selective detection in flow analysis based on the combination of immobilized enzymes and chemically modified electrodes," *Analytica Chimica Acta.,* 250:203–248 (1991).

Gregg, B. A. et al., "Cross–Linked Redox Gels Containing Glucose Oxidase for Amperometric Biosensor Applications," *Analytical Chemistry,* 62(3):258–263 (Feb. 1, 1990).

Gregg, B. A. et al., "Redox Polymer Films Containing Enzymes. 1. A Redox–Conducting Epoxy Cement: Synthesis, Characterization, and Electrocatalytic Oxidation of Hydroquinone," *J. Phys. Chem.,* 95(15):5970–5975 (1991).

Hale, P D et al., "A New Class of Amperometric Biosensor Incorporating a Polymeric Electron–Transfer Mediator," *J. Am. Chem. Soc.,* 111(9):3482–3484 (1989).

Harrison, D.J. et al., "Characterization of Perfluorosulfonic Acid Polymer Coated Enzyme Electrodes and a Miniaturized Integrated Potentiostat for Glucose Analysis in Whole Blood", *Anal. Chem.,* 60(19):2002–2007 (Oct. 1, 1988).

Hawkridge, F. M. et al., "Indirect Coulometric Titration of Biological Electron Transport Components," *Analytical Chemistry,* 45(7):1021–1027 (Jun. 1973).

Heller, A., "Amperometric biosensors based on three–dimensional hydrogel–forming epoxy networks," *Sensors and Actuators B.* 13–14:180–183 (1993).

Heller, A., "Electrical Connection of Enzyme Redox Centers to Electrodes," *J. Phys. Chem.,* 96(9):3579–3587 (1992).

Heller, A., "Electrical Wiring of Redox Enzymes," *Acc. Chem. Res.,* 23(5):129–134 (1990).

Ianniello, R.M. et al. "Immobilized Enzyme Chemically Modified Electrode as an Amperometric Sensor", *Anal. Chem.,* 53(13):2090–2095 (Nov. 1981).

Ianniello, R.M. et al., "Differential Pulse Voltammetric Study of Direct Electron Transfer in Glucose Oxidase Chemically Modified Graphite Electrodes", *Anal. Chem.,* 54(7):1098–1101 (Jun. 1981).

Ikeda, T. et al., "Glucose oxidase–immobilized benzoquinone–carbon paste electrode as a glucose sensor," *Agric. Biol. Chem.,* 49(2) (1 page—Abstract only) (1985).

Ikeda, T. et al., "Kinetics of Outer–Sphere Electron Transfers Between Metal Complexes in Solutions and Polymeric Films on Modified Electrodes", *J. Am. Chem. Soc.,* 103(25):7422–7425 (Dec. 16, 1981).

Johnson, J. M. et al., "Potential–Dependent Enzymatic Activity in an Enzyme Thin–Layer Cell," *Anal. Chem.* 54:1377–1383 (1982).

Johnson, K. W., "Reproducible Electrodeposition of Biomolecules for the Fabrication of Miniature Electroenzymatic Biosensors", *Sensors and Actuators B Chemical,* B5:85–89 (1991).

Jonsson, G. et al., "An Amperometric Glucose Sensor Made by Modification of a Graphite Electrode Surface With Immobilized Glucose Oxidase and Adsorbed Mediator", *Biosensors,* 1:355–368 (1985).

Josowicz, M. et al., "Electrochemical Pretreatment of Thin Film Platinum Electrodes", *J. Electrochem. Soc.,* 135(1):112–115 (Jan. 1988).

Katakis, I. et al., "Electrostatic Control of the Electron Transfer Enabling Binding of Recombinant Glucose Oxidase and Redox Polyelectrolytes," *J. Am. Chem. Soc.,* 116(8):3617–3618 (1994).

Katakis, I. et al., "L–α–Glycerophosphate and L–Lactate Electrodes Based on the Electrochemical "Wiring" of Oxidases," *Analytical Chemistry,* 64(9):1008–1013 (May 1, 1992).

Kenausis, G. et al., "Wiring of glucose oxidase and lactate oxidase within a hydrogel made with poly(vinyl pyridine) complexed with $[Os(4,4'–dimethoxy–2,2'–bipyridine)_2C1]^{+/2+}$," *J. Chem. Soc., Faraday Trans.,* 90(20):4131–4136 (1996).

Koudelka, M. et al., "In–Vivo Behaviour of Hypodermically Implanted Microfabricated Glucose Sensors", *Biosensors & Bioelectronics,* 6(1):31–36 (1991).

Kulys, J. et al., "Mediatorless peroxidase electrode and preparation of bienzyme sensors," *Bioelectrochemistry and Bioenergetics,* 24:305–311 (1990).

Lager, W. et al., "Implantable Electrocatalytic Glucose Sensor," *Horm. Metab. Res.,* 26:526–530 (Nov. 1994).

Lindner, E. et al. "Flexible (Kapton–Based) Microsensor Arrays of High Stability for Cardiovascular Applications", *J. Chem. Soc, Faraday Trans.,* 89(2):361–367 (Jan. 21, 1993).

Maidan, R. et al., "Elimination of Electrooxidizable Interferant–Produced Currents in Amperometric Biosensors," *Analytical Chemistry,* 64(23):2889–2896 (Dec. 1, 1992).

Mastrototaro, J.J. et al., "An Electroenzymatic Glucose Sensor Fabricated on a Flexible Substrate", *Sensors and Biosensors B Chemical,* B5:139–144 (1991).

McNeil, C. J. et al., "Thermostable Reduced Nicotinamide Adenine Dinucleotide Oxidase: Application to Amperometric Enzyme Assay," *Anal. Chem.,* 61(1):25–29 (Jan. 1, 1989).

Miyawaki, O. et al., "Electrochemical and Glucose Oxidase Coenzyme Activity of Flavin Adenine Dinucleotide Covalently Attached to Glassy Carbon at the Adenine Amino Group", *Biochimica et Biophysica Acta,* 838:60–68 (1985).

Moatti–Sirat, D. et al., "Evaluating in vitro and in vivo the inteference of ascorbate and acetaminophen on glucose detection by a needle–type glucose sensor," *Biosensors & Bioelectronics,* 7(5):345–352 (1992).

Moatti–Sirat, D. et al., "Reduction of acetaminophen interference in glucose sensors by a composite Nafion membrane: demonstration in rats and man," *Diabetologia,* 37(6) (1 page—Abstract only) (Jun. 1994).

Moatti–Sirat, D. et al., "Towards continuous glucose monitoring: in vivo evaluation of a miniaturized glucose sensor implanted for several days in rat subcutaneous tissue," *Diabetologia,* 35(3) (1 page—Abstract only) (Mar. 1992).

Nagy, G. et al., "A New Type of Enzyme Electrode: The Ascorbic Acid Eliminator Electrode," *Life Sciences,* 31(23):2611–2616 (1982).

Nakamura, S. et al., "Effect of Periodate Oxidation on the Structure and Properties of Glucose Oxidase," *Biochimica et Biophysica Acta.,* 445:294–308 (1976).

Narazimhan, K. et al., "p–Benzoquinone activation of metal oxide electrodes for attachment of enzymes," *Enzyme Microb. Technol.,* 7(6) (1 page—Abstract only) (1985).

Ohara, T. J. et al., "Glucose Electrodes Based on Cross–Linked $[Os(bpy)_2C1]^{+/2+}$ Complexed Poly(1–vinylimadazole) Films," *Analytical Chemistry,* 65(23):3512–3516 (Dec. 1, 1993).

Ohara, T. J., "Osmium Bipyridyl Redox Polymers Used in Enzyme Electrodes," *Platinum Metals Rev.,* 39(2):54–62 (Apr. 1995).

Ohara, T. J. et al., ""Wired" Enzyme Electrodes for Amperometric Determination of Glucose or Lactate in the Presence of Interfering Substances," *Analytical Chemistry,* 66(15):2451–2457 (Aug. 1, 1994).

Olievier, C. N. et al., "In vivo Measurement of Carbon Dioxide Tension with a Miniature Electrode," *Pflugers Arch.* 373:269–272 (1978).

Paddock, R. et al., "Electrocatalytic reduction of hydrogen peroxide via direct electron transfer from pyrolytic graphite electrodes to irreversibly adsorbed cytochrome c peroxidase," *J. Electroanal. Chem.,* 260:487–494 (1989).

Palleschi, G. et al., "A Study of Interferences in Glucose Measurements in Blood by Hydrogen Peroxide Based Glucose Probes", *Anal. Biochem.,* 159:114–121 (1986).

Pankramov, I. et al., "Sol–gel derived renewable–surface biosensors," *Journal of Electroanalytical Chemistry,* 393:35–41 (1995).

Pathak, C. P. et al., "Rapid Photopolymerization of Immunoprotective Gels in Contact with Cells and Tissue," *J. Am. Chem. Soc.,* 114(21):8311–8312 (1992).

Pickup, J., "Developing glucose sensors for in vivo use," *Tibtech,* 11:285–289 (Jul. 1993).

Pickup, J. C. et al., "In vivo molecular sensing in diabetes mellitus: an implantable glucose sensor with direct electron transfer," *Diabetologia,* 32(3):213–217 (1989).

Pickup, J. et al., "Potentially–implantable, amperometric glucose sensors with mediated electron transfer: improving the operating stability," *Biosensors,* 4(2) (1 page—Abstract only) (1989).

Pishko, M.V. et al., "Amperometric Glucose Microelectrodes Prepared Through Immobilization of Glucose Oxidase in Redox Hydrogels", *Anal. Chem.,* 63(20):2268–2272 (Oct. 15, 1991).

Poitout, V. et al., "A glucose monitoring system for on line estimation in man of blood glucose concentration using a miniaturized glucose sensor implanted in the subcutaneous tissue and a wearable control unit," *Diabetologia,* 36(7) (1 page—Abstract only) (Jul. 1993).

Poitout, V. et al., "Calibration in dogs of a subcutaneous miniaturized glucose sensor using a glucose meter for blood glucose determination," *Biosensors & Bioelectronics,* 7:587–592 (1992).

Poitout, V. et al., "In vitro and in vivo evaluation in dogs of a miniaturized glucose sensor," *ASAIO Transactions,* 37(3) (1 page—Abstract only) (Jul.–Sep. 1991).

Pollak, A. et al., "Enzyme immobilization by Condensation Copolymerization into Cross–Linked Polyacrylamide Gels," *J. Am. Chem. Soc.,* 102(20):6324–6336 (1980).

Reach, G. et al., "Can Continuous Glucose Monitoring Be Used for the Treatment of Diabetes?" *Analytical Chemistry,* 64(6):381–386 (Mar. 15, 1992).

Rebrin, K. et al., "Automated Feedback Control of subcutaneous Glucose Concentration in Diabetic Dogs", *Diabetologia,* 32(8):573–576 (Aug. 1989).

Sakakida, M. et al., "Ferrocene–mediate needle–type glucose sensor covered with newly designed biocompatible membrane," *Sensors and Actuators B,* 13–14:319–322 (1993).

Samuels, G. J. et al., "An Electrode–Supported Oxidation Catalyst Based on Ruthenium (IV). pH "Encapsulation" in a Polymer Film," *J. Am. Chem. Soc.,* 103(2):307–312 (1981).

Sasso, S.V. et al., "Electropolymerized 1,2–Diaminobenzene as a Means to Prevent Interferences and Fouling and to Stabilize Immobilized Enzyme in Electrochemical Biosensors", *Anal. Chem.,* 62(11):1111–1117 (Jun. 1, 1990).

Scheller, F. et al., "Enzyme electrodes and their application," *Phil. Trans. R Soc. Lond.,* B 316:85–94 (1987).

Schmehl, R.H. et al., "The Effect of Redox Site Concentration on the Rate of Mediated Oxidation of Solution Substrates by a Redox Copolymer Film", *J. Electroanal. Chem.,* 152:97–109 (Aug. 25, 1983).

Shichiri, M. et al., "Glycaemic Control in Pancrearetomized Dogs with a Wearable Artificial Endocrine Pancreas", *Diabetologia,* 24(3):179–184 (Mar. 1983).

Sirtampalam, G. et al., "Surface–Modified Electrochemical Detector for Liquid Chromatography", *Anal. Chem.,* 55(9):1608–1610 (Aug. 1983).

Soegijoko, S. et al., *Horm. Metabl. Res., Suppl. Ser.* 12 (1 page—Abstract only) (1982).

Sprules, S. D. et al., "Evaluation of a New Disposable Screen–Printed Sensor Strip for the Measurement of NADH and Its Modification to Produce a Lactate Biosensor Employing Microliter Volumes," *Electroanalysis,* 8(6):539–543 (1996).

Sternberg, F. et al., "Calibration Problems of Subcutaneous Glucosensors when Applied "In–Situ" in Man," *Horm. metabl. Res.* 26:524–525 (1994).

Sternberg, R. et al., "Covalent Enzyme Coupling on Cellulose Acetate Membranes for Glucose Sensor Development," *Analytical Chemistry,* 60(24):2781–2786 (Dec. 15, 1988).

Sternberg, R. et al., "Study and Development of Multilayer Needle–type Enzyme–based Glucose Microsensors," *Biosensors,* 4:27–40 (1988).

Suckane, M., "Immobilization of glucose isomerase," *Zeitschrift fur Allgemeine Mikrobiologie,* 22(8):565–576 (1982).

Tajima, S. et al., "Simultaneous Determination of Glucose and 1,5–Anydroglucitol", *Chemical Abstracts,* 111(25):394 111:228556g (Dec. 18, 1989).

Tarasevich, M.R. "Bioelectrocatalysis", *Comprehensive Treasige of Electrochemistry,* 10 (Ch. 4):231–295 (1985).

Tatsuma, T. et al., "Enzyme Monolayer– and Bilayer–Modified Tin Oxide Electrodes for the Determination of Hydrogen Peroxide and Glucose," *Anal. Chem.,* 61(21):2352–2355 (Nov. 1, 1989).

Taylor, C. et al., "'Wiring' of glucose oxidase within a hydrogel made with polyvinyl imidazole complexed with $[(Os–4,4'–dimethoxy–2,2'–bipyridine)C1]^{+/2+}$," *Journal of Electroanalytical Chemistry,* 396:511–515 (1995).

Trojanowicz, M. et al., "Enzyme Entrapped Polypyrrole Modified Electrode for Flow–Injection Determination of Glucose," *Biosensors & Bioelectronics,* 5:149–156 (1990).
Turner, A.P.F. et al., "Diabetes Mellitus: Biosensors for Research and Management", *Biosensors,* 1:85–115 (1985).
Turner, R.F.B. et al., "A Biocompatible Enzyme Electrode for Continuous in vivo Glucose Monitoring in Whole Blood," *Sensors and Actuators,* B1(1–6):561–564 (Jan. 1990).
Tuzhi, P. et al., "Constant Potential Pretreatment of Carbon Fiber Electrodes for In vivo Electrochemistry", *Analytical Letters,* 24(6):935–945 (1991).
Umaha, M., "Protein–Modified Electrochemically Active Biomaterial Surface," *U S. Army Research Office Report,* (12 pages) (Dec. 1988).
Urban, G. et al., "Miniaturized Thin–Film Biosensors Using Covalently Immobilized Glucose Oxidase", *Biosensors & Bioelectronics,* 6(7):555–562 (1991).
Velho, G. et al., "In Vitro and In Vivo Stability of Electrode Potentials in Needle–Type Glucose Sensors", *Diabetes,* 38(2):164–171 (Feb. 1989).
Velho, G. et al., "Strategies for calibrating a subcutaneous glucose sensor," *Biomed. Biochim. Acta,* 48(11/12);957–964 (1989).
Von Woedtke, T. et al., "In Situ Calibration of Implanted Electrochemical Glucose Sensors," *Biomed. Biochim. Acta,* 48(11/12):943–952 (1989).
Vrecke, M. S. et al., "Chapter 15: Hydrogen Peroxide Electrodes Based on Electrical Connection of Redox Centers of Various Peroxidases to Electrodes through a Three–Dimensional Electron–Relaying Polymer Network," *Diagnostic Biosensor Polymers,* 7 pgs. (Jul. 26, 1993).
Vrecke, M. et al., "Hydrogen Peroxide and β–Nicotinamide Adenine Dinucleotide Sensing Amperometric Electrodes Based on Electrical Connection of Horseradish Peroxidase Redox Centers to Electrodes through a Three–Dimensional Electron Relaying Polymer Network," *Analytical Chemistry,* 64(24):3084–3090 (Dec. 15, 1992).
Wang, J. et al., "Activation of Glassy Carbon Electrodes by Alternating Current Electrochemical Treatment", *Analytica Chimica Acta,* 167:325–334 (Jan. 1985).
Wang, J. et al., "Amperometric biosensing of organic peroxides with peroxidase–modified electrodes," *Analytica Chimica Acta.* 254:81–88 (1991).
Wang, D. L. et al., "Miniaturized Flexible Amperometric Lactate Probe," *Analytical Chemistry,* 65(8):1069–1073 (Apr. 15, 1993).
Wang, J. et al., "Screen–Printable Sol–Gel Enzyme–Containing Carbon Inks," *Analytical Chemistry,* 68(15):2705–2708 (Aug. 1, 1996).
Wang, J. et al., "Sol–Gel–Derived Metal–Dispersed Carbon Composite Amperometric Biosensors," *Electroanalysis,* 9(1):52–55 (1997).
Williams, D.L. et al., "Electrochemical–Enzymatic Analysis of Blood Glucose and Lactate", *Anal. Chem.,* 42(1):118–121 (Jan. 1970).
Wilson, G. S. et al., "Progress toward the Development of an Implantable Sensor for Glucose," *Clinical Chemistry,* 38(9):1613–1617 (1992).
Yabuki, S. et al., "Electro–conductive Enzyme Membrane," *J. Chem. Soc. Commun,* 945–946 (1989).
Yang, I. et al., "Determination of Oxidase Enzyme Substrates Using Cross–Flow Thin–Layer Amperometry," *Electroanalysis,* 8(8–9):716–721 (1996).
Yao, S.J. et al., "The Interference of Ascorbate and Urea in Low–Potential Electrochemical Glucose Sensing", *Proceedings of the Twelfth Annual International Conference of the IEEE Engineering in Medicine and Biology Society,* 12(2):487–489 (Nov. 1–4, 1990).
Yao, T. et al., "A Chemically–Modified Enzyme Membrane Electrode As An Amperometric Glucose Sensor," *Analytica Chimica Acta.,* 148:27–33 (1983).
Ye, L. et al., "High Current Density "Wired" Quinoprotein Glucose Dehydrogenase Electrode," *Anal. Chem.,* 65(3):238–241 (Feb. 1, 1993).
Yildiz, A. et al., "Evaluation of an Improved Thin–Layer Electrode," *Analytical Chemistry,* 40(70):1018–1024 (Jun. 1968).
Zamzow, K. et al., New Wearable Continuous Blood Glucose Monitor (BGM) and Artificial Pancreas (AP), *Diabetes,* 39:5A(20) (May 1990).
Zhang, Y. et al., "Application of cell culture toxicity tests to the development of implantable biosensors," *Biosensors & Bioelectronics,* 6:653–661 (1991).
Zhang, Y. et al., "Elimination of the Acetaminophen Interference in an Implantable Glucose Sensor," *Anal. Chem,* 66:1183–1188 (1994).

* cited by examiner

EXHIBIT 6

US006284478B1

(12) **United States Patent**
Heller et al.

(10) **Patent No.: US 6,284,478 B1**
(45) **Date of Patent: *Sep. 4, 2001**

(54) **SUBCUTANEOUS GLUCOSE ELECTRODE**

(75) Inventors: **Adam Heller**; **Michael V. Pishko**, both of Austin, TX (US)

(73) Assignee: **E. Heller & Company**, Alameda, CA (US)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/767,110**

(22) Filed: **Dec. 4, 1996**

Related U.S. Application Data

(63) Continuation of application No. 08/299,526, filed on Sep. 1, 1994, now Pat. No. 5,593,852, which is a continuation-in-part of application No. 08/161,682, filed on Dec. 2, 1993, now Pat. No. 5,356,786.

(51) **Int. Cl.**[7] **C12Q 1/54**; C12Q 1/00; C12Q 1/26; C12Q 1/28

(52) **U.S. Cl.** **435/14**; 435/4; 435/25; 435/28; 435/817; 435/287; 436/63; 436/149; 204/403

(58) **Field of Search** 435/4, 14, 25, 435/28, 817, 287; 436/63, 149; 204/403

(56) **References Cited**

U.S. PATENT DOCUMENTS

Re. 32,947	6/1989	Dormer et al.	435/14
3,260,656	7/1966	Ross, Jr.	435/14
3,653,841	4/1972	Klein	435/14
3,719,564	3/1973	Lilly, Jr. et al.	435/14
3,776,832	12/1973	Oswin et al.	435/14
3,837,339	9/1974	Aisenberg et al.	435/14
3,926,760	12/1975	Allen et al.	435/14
3,972,320	8/1976	Kalman	435/14
3,979,274	9/1976	Newman	435/14
4,008,717	2/1977	Kowarski	435/14

(List continued on next page.)

FOREIGN PATENT DOCUMENTS

227 029 A3	9/1985	(DD) .
29 03 216	8/1979	(DE) .
3934299	10/1990	(DE) .
44 01 400 A1	7/1995	(DE) .
0 010 375 A1	4/1980	(EP) .

(List continued on next page.)

OTHER PUBLICATIONS

Abruña, II. D. et al., "Rectifying Interfaces Using Two–Layer Films of Electrochemically Polymerized Vinylpyridine and Vinylbipyridine Complexes of Ruthenium and Iron on Electrodes," *J. Am. Chem. Soc.*, 103(1):1–5 (Jan. 14, 1981).

Albery, W. J. et al., "Amperometric enzyme electrodes. Part II. Conducting salts as electrode materials for the oxidation of glucose oxidase," *J. Electroanal. Chem. Interfacial Electrochem.*, 194(2)(1 page–13 Abstract only)(1985).

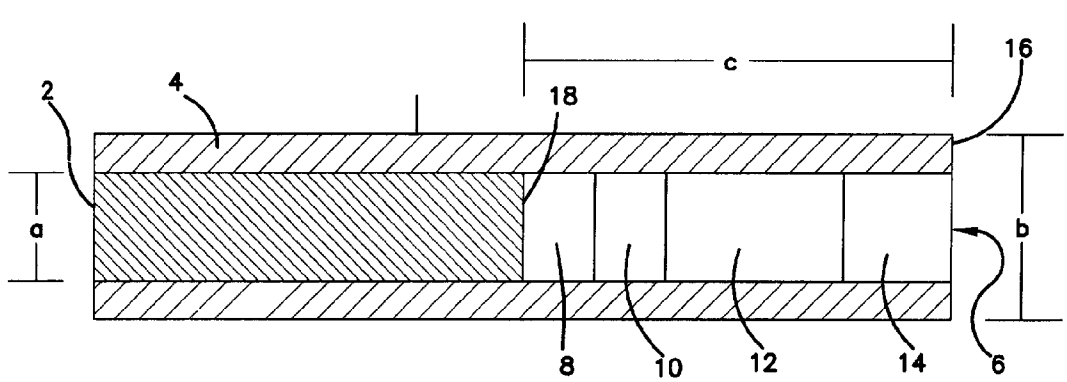
(List continued on next page.)

Primary Examiner—Louise N. Leary
(74) *Attorney, Agent, or Firm*—Merchant & Gould P.C.

(57) **ABSTRACT**

A small diameter flexible electrode designed for subcutaneous in vivo amperometric monitoring of glucose is described. The electrode is designed to allow "one-point" in vivo calibration, i.e., to have zero output current at zero glucose concentration, even in the presence of other electroreactive species of serum or blood. The electrode is preferably three or four-layered, with the layers serially deposited within a recess upon the tip of a polyamide insulated gold wire. A first glucose concentration-to-current transducing layer is overcoated with an electrically insulating and glucose flux limiting layer (second layer) on which, optionally, an immobilized interference-eliminating horseradish peroxidase based film is deposited (third layer). An outer (fourth) layer is biocompatible.

74 Claims, 10 Drawing Sheets



U.S. PATENT DOCUMENTS

4,016,866	4/1977	Lawton	435/14
4,055,175	10/1977	Clemens et al.	435/14
4,059,406	11/1977	Fleet	435/14
4,076,596	2/1978	Connery et al.	435/14
4,098,574	7/1978	Dappen	435/14
4,100,048	7/1978	Pompei et al.	435/14
4,151,845	5/1979	Clemens	435/14
4,168,205	9/1979	Danninger et al.	435/14
4,172,770	10/1979	Semersky et al.	435/14
4,178,916	12/1979	McNamara	435/14
4,206,755	6/1980	Klein	435/14
4,224,125	9/1980	Nakamura et al.	435/14
4,240,438	12/1980	Updike et al.	435/14
4,247,297	1/1981	Berti et al.	435/14
4,340,458	7/1982	Lerner et al.	435/14
4,352,960	10/1982	Dormer et al.	435/14
4,356,074	10/1982	Johnson	435/14
4,365,637	12/1982	Johnson	435/14
4,366,033	12/1982	Richter et al.	435/14
4,375,399	3/1983	Havas et al.	435/14
4,384,586	5/1983	Christiansen	435/14
4,390,621	6/1983	Bauer	435/14
4,401,122	8/1983	Clark, Jr.	435/14
4,404,066	9/1983	Johnson	435/14
4,418,148	11/1983	Oberhardt	435/14
4,427,770	1/1984	Chen et al.	435/14
4,431,004	2/1984	Bessman et al.	435/14
4,436,094	3/1984	Cerami	435/14
4,440,175	4/1984	Wilkins	435/14
4,450,842	5/1984	Zick et al.	435/14
4,458,686	7/1984	Clark, Jr.	435/14
4,461,691	7/1984	Frank	435/14
4,469,110	9/1984	Slama	435/14
4,477,314	10/1984	Richter et al.	435/14
4,484,987	11/1984	Gough	435/14
4,522,690	6/1985	Venkatasetty	435/14
4,524,114	6/1985	Samuels et al.	435/14
4,526,661	7/1985	Steckhan et al.	435/14
4,534,356	8/1985	Papadakis	435/14
4,538,616	9/1985	Rogoff	435/14
4,543,955	10/1985	Schroeppel	435/14
4,545,382	10/1985	Higgins et al.	435/14
4,552,840	11/1985	Riffer	435/14
4,560,534	12/1985	Kung et al.	435/14
4,571,292	2/1986	Liu et al.	435/14
4,573,994	3/1986	Fischell et al.	435/14
4,581,336	4/1986	Malloy et al.	435/14
4,595,011	6/1986	Phillips	435/14
4,619,754	10/1986	Niki et al.	435/14
4,627,445	12/1986	Garcia et al.	435/14
4,627,908	12/1986	Miller	435/14
4,633,878	1/1987	Bombardieri	435/14
4,637,403	1/1987	Garcia et al.	435/14
4,650,547	3/1987	Gough	435/14
4,654,197	3/1987	Lilja et al.	435/14
4,655,880	4/1987	Liu	435/14
4,655,885	4/1987	Hill et al.	435/14
4,671,288	6/1987	Gough	435/14
4,679,562	7/1987	Luksha	435/14
4,680,268	7/1987	Clark, Jr.	435/14
4,682,602	7/1987	Prohaska	435/14
4,684,537	8/1987	Graetzel et al.	435/14
4,685,463	8/1987	Williams	435/14
4,703,756	11/1987	Gough et al.	435/14
4,711,245	12/1987	Higgins et al.	435/14
4,717,673	1/1988	Wrighton et al.	435/14
4,721,601	1/1988	Wrighton et al.	435/14
4,721,677	1/1988	Clark, Jr.	435/14
4,726,378	2/1988	Kaplan	435/14
4,726,716	2/1988	McGuire	435/14
4,757,022	7/1988	Shults et al.	435/14
4,758,323	7/1988	Davis et al.	435/14
4,759,371	7/1988	Franetzki	435/14
4,759,828	7/1988	Young et al.	435/14
4,764,416	8/1988	Ueyama et al.	435/14
4,776,944	10/1988	Janata et al.	435/14
4,777,953	10/1988	Ash et al.	435/4
4,781,798	11/1988	Gough	435/14
4,784,736	11/1988	Lonsdale et al.	435/14
4,795,707	1/1989	Niiyama et al.	435/14
4,796,634	1/1989	Huntsman et al.	435/14
4,805,624	2/1989	Yao et al.	435/14
4,813,424	3/1989	Wilkins	435/14
4,815,469	3/1989	Cohen et al.	435/14
4,820,399	4/1989	Senda et al.	435/14
4,822,337	4/1989	Newhouse et al.	435/14
4,830,959	5/1989	McNeil et al.	435/14
4,832,797	5/1989	Vadgama et al.	435/14
4,840,893	6/1989	Hill et al.	435/14
4,848,351	7/1989	Finch	435/14
4,854,322	8/1989	Ash et al	435/4
4,871,351	10/1989	Feingold	435/14
4,871,440	10/1989	Nagata et al.	435/14
4,874,500	10/1989	Madou et al.	435/14
4,890,620	1/1990	Gough	435/14
4,894,137	1/1990	Takizawa et al.	435/14
4,897,162	1/1990	Lewandowski et al.	435/14
4,897,173	1/1990	Nankai et al.	435/14
4,909,908	3/1990	Ross et al.	435/14
4,911,794	3/1990	Parce et al.	435/14
4,917,800	4/1990	Lonsdale et al.	435/14
4,919,141	4/1990	Zier et al.	435/14
4,919,767	4/1990	Vadgama et al.	435/14
4,923,586	5/1990	Katayama et al.	435/14
4,927,516	5/1990	Yamaguchi et al.	435/14
4,934,369	6/1990	Maxwell	435/14
4,935,105	6/1990	Churchouse	435/14
4,935,345	6/1990	Guilbeau et al.	435/14
4,938,860	7/1990	Wogoman	435/14
4,944,299	7/1990	Silvian	435/14
4,950,378	8/1990	Nagata	435/14
4,953,552	9/1990	DeMarzo	435/14
4,954,129	9/1990	Giuliani et al.	435/14
4,969,468	11/1990	Byers et al.	435/14
4,970,145	11/1990	Bennetto et al.	435/14
4,974,929	12/1990	Curry	435/14
4,986,271	1/1991	Wilkins	435/14
4,994,167	2/1991	Shults et al.	435/14
5,001,054	3/1991	Wagner	435/14
5,002,054	3/1991	Ash et al.	435/4
5,058,592	10/1991	Whisler	435/14
5,070,535	12/1991	Hochmair et al.	435/14
5,082,550	1/1992	Rishpon et al.	435/14
5,082,786	1/1992	Nakamoto	435/14
5,089,112	2/1992	Skotheim et al.	435/14
5,095,904	3/1992	Seligman et al.	435/14
5,101,814	4/1992	Palti	435/14
5,106,365	4/1992	Hernandez	435/4
5,108,564	4/1992	Szuminsky et al.	435/14
5,109,850	5/1992	Blanco et al.	435/14
5,120,420	6/1992	Nankai et al.	435/14
5,126,034	6/1992	Carter et al.	435/14
5,133,856	7/1992	Yamaguchi et al.	435/14
5,135,003	8/1992	Souma	435/14
5,141,868	8/1992	Shanks et al.	435/14
5,161,532	11/1992	Joseph	435/14
5,165,407	11/1992	Wilson et al.	435/14
5,174,291	12/1992	Schoonen et al.	435/14
5,190,041	3/1993	Palti	435/14
5,192,416	3/1993	Wang et al.	435/14
5,198,367	3/1993	Aizawa et al.	435/14
5,202,261	4/1993	Musho et al.	435/14

5,205,920	4/1993	Oyama et al.	435/14
5,208,154	5/1993	Weaver et al.	435/14
5,209,229	5/1993	Gilli	435/14
5,217,595	6/1993	Smith et al.	435/14
5,229,282	7/1993	Yoshioka et al.	435/14
5,250,439	10/1993	Musho et al.	435/14
5,262,035	11/1993	Gregg et al.	435/14
5,262,305	11/1993	Heller et al.	435/14
5,264,103	11/1993	Yoshioka et al.	435/14
5,264,104	11/1993	Gregg et al.	435/14
5,264,106	11/1993	McAleer et al.	435/14
5,271,815	12/1993	Wong	435/14
5,279,294	1/1994	Anderson et al.	435/14
5,286,362	2/1994	Hoenes et al.	435/14
5,286,364	2/1994	Yacynych et al.	435/14
5,288,636	2/1994	Pollmann et al.	435/14
5,293,546	3/1994	Tadros et al.	435/14
5,320,098	6/1994	Davidson	435/14
5,320,725	6/1994	Gregg et al.	435/14
5,322,063	6/1994	Allen et al.	435/14
5,337,747	8/1994	Neftel	435/14
5,352,348	10/1994	Young et al.	435/14
5,356,786	10/1994	Heller et al.	435/14
5,368,028	11/1994	Palti	435/14
5,372,133	12/1994	Hogen Esch	435/14
5,376,251	12/1994	Kaneko et al.	435/14
5,378,628	1/1995	Grätzel et al.	435/14
5,387,327	2/1995	Khan	435/14
5,390,671	2/1995	Lord et al.	435/14
5,391,250	2/1995	Cheney, II et al.	435/14
5,395,504	3/1995	Saurer et al.	435/14
5,411,647	5/1995	Johnson et al.	435/14
5,437,999	8/1995	Diebold et al.	435/14
5,462,645	10/1995	Albery et al.	435/4
5,469,846	11/1995	Khan	435/14
5,494,562	2/1996	Maley et al.	435/14
5,496,453	3/1996	Uenoyama et al.	435/14
5,497,772	3/1996	Schulman et al.	435/14
5,531,878	7/1996	Vadgama et al.	435/14
5,545,191	8/1996	Mann et al.	435/14
5,560,357	10/1996	Faupel et al.	435/14
5,565,085	10/1996	Ikeda et al.	435/14
5,567,302	10/1996	Song et al.	435/14
5,568,806	10/1996	Cheney, II et al.	435/14
5,569,186	10/1996	Lord et al.	435/14
5,582,184	12/1996	Erickson et al.	435/14
5,582,697	12/1996	Ikeda et al.	435/14
5,582,698	12/1996	Flaherty et al.	435/14
5,586,553	12/1996	Halili et al.	435/14
5,589,326	12/1996	Deng et al.	435/14
5,593,852	1/1997	Heller et al.	435/14
5,596,150	1/1997	Arndt et al.	435/14
5,617,851	4/1997	Lipkovker	435/14
5,628,890	5/1997	Carter et al.	435/14
5,651,869	7/1997	Yoshioka et al.	435/14
5,660,163	8/1997	Schulman et al.	435/14
5,670,031	9/1997	Hintsche et al.	435/14
5,680,858	10/1997	Hansen et al.	435/14
5,682,233	10/1997	Brinda	435/14
5,695,623	12/1997	Michel et al.	435/14
5,708,247	1/1998	McAleer et al.	435/14
5,711,861	1/1998	Ward et al.	435/14
5,711,862	1/1998	Sakoda et al.	435/14
5,741,211	4/1998	Renirie et al.	435/14
5,791,344	8/1998	Schulman et al.	435/14

FOREIGN PATENT DOCUMENTS

0 026 995 A1	4/1981	(EP) .
0 048 090 A2	3/1982	(EP) .
0 078 636 A1	5/1983	(EP) .
0 096 288 A1	12/1983	(EP) .
0 125 139 A2	11/1984	(EP) .
0 127 958 A2	12/1984	(EP) .
0 136 362 A1	4/1985	(EP) .
0 170 375 A2	2/1986	(EP) .
0 177 743 A2	4/1986	(EP) .
0 080 304 B1	5/1986	(EP) .
0 184 909 A2	6/1986	(EP) .
0 206 218 A2	12/1986	(EP) .
0 230 472 A1	8/1987	(EP) .
0 241 309 A3	10/1987	(EP) .
0 245 073 A2	11/1987	(EP) .
0 278 647 A2	8/1988	(EP) .
0 359 831 A1	3/1990	(EP) .
0 368 209 A1	5/1990	(EP) .
0 390 390 A1	10/1990	(EP) .
0 400 918 A1	12/1990	(EP) .
0 453 283 A1	10/1991	(EP) .
0 470 290 A1	2/1992	(EP) .
0 127 958 B2	3/1992	(EP) .
0 255 291 B1	6/1992	(EP) .
1394171	5/1975	(GB) .
1599241	9/1981	(GB) .
2 073 891	10/1981	(GB) .
2 154 003	2/1988	(GB) .
2 204 408	11/1988	(GB) .
2 254 436	10/1992	(GB) .
54-41191	4/1979	(JP) .
55-10581	1/1980	(JP) .
55-10583	1/1980	(JP) .
55-10584	1/1980	(JP) .
55-12406	1/1980	(JP) .
56-163447	12/1981	(JP) .
57-70448	4/1982	(JP) .
60-173457	9/1985	(JP) .
60-173458	9/1985	(JP) .
60-173459	9/1985	(JP) .
61-90050	5/1986	(JP) .
62-85855	4/1987	(JP) .
62-114747	5/1987	(JP) .
63-58149	3/1988	(JP) .
63-128252	5/1988	(JP) .
63-139246	6/1988	(JP) .
63-294799	12/1988	(JP) .
63-317757	12/1988	(JP) .
63-317758	12/1988	(JP) .
1-114746	5/1989	(JP) .
1-114747	5/1989	(JP) .
1-124060	5/1989	(JP) .
1-134244	5/1989	(JP) .
1-156658	6/1989	(JP) .
2-62958	3/1990	(JP) .
2-120655	5/1990	(JP) .
2-287145	11/1990	(JP) .
2-310457	12/1990	(JP) .
3-26956	2/1991	(JP) .
3-28752	2/1991	(JP) .
3-202764	9/1991	(JP) .
5-72171	3/1993	(JP) .
5-196595	8/1993	(JP) .
7-72585	3/1995	(JP) .
1281988 A1	1/1987	(SU) .
WO 85/05119	11/1985	(WO) .
89/08713	9/1989	(WO) .
90/05300	5/1990	(WO) .
90/05910	5/1990	(WO) .
91/01680	2/1991	(WO) .
91/04704	4/1991	(WO) .
91/15993	10/1991	(WO) .
92/13271	8/1992	(WO) .
94/20602	9/1994	(WO) .
94/27140	11/1994	(WO) .
96/30431	10/1996	(WO) .
WO 96/30431	10/1996	(WO) .

97/02847 1/1997 (WO) .
97/19344 5/1997 (WO) .
97/42882 11/1997 (WO) .
97/42883 11/1997 (WO) .
97/42886 11/1997 (WO) .
97/42888 11/1997 (WO) .
97/43962 11/1997 (WO) .

OTHER PUBLICATIONS

Albery, W. J. et al., "Amperometric Enzyme Electrodes," *Phil. Trans. R. Soc. Lond.* B316:107–119 (1987).

Alcock, S. J. et al., "Continuous Analyte Monitoring to Aid Clinical Practice," *IEEE Engineering in Medicine and Biology*, 319–325 (1994).

Anderson, L. B. et al., "Thin–Layer Electrochemistry: Steady–State Methods of Studying Rate Processes," *J. Electroanal. Chem.*, 10:295–395 (1965).

Bartlett, P. N. et al., "Covalent Binding of Electron Relays to Glucose Oxidation," *J. Chem. Soc. Chem. Commun.*, 1603–1604 (1987).

Bartlett, P. N. et al., "Modification of glucose oxidase by tetrathiafulvalene," *J. Chem. Soc., Chem. Commun.*, 16 (1 page–Abstract only) (1990).

Bartlett, P. N. et al., "Strategies for the Development of Amperometric Enzyme Electrodes," *Biosensors*, 3:359–379 (1987/88).

Bindra, D.S. et al., "Design and in Vitro Studies of a Needle–Type Glucose Sensor for Subcutaneous Monitoring", *Anal. Chem.*, 63(17):1692–1696 (Sep. 1, 1991).

Bobbioni–Harsch, E. et al., "Lifespan of subcutaneous glucose sensors and their performances during dynamic glycaemia changes in rats," *J. Biomed. Eng.* 15:457–463 (1993).

Brandt, J. et al., "Covalent attachment of proteins to polysaccharide carriers by means of benzoquinone," *Biochim. Biophys. Acta*, 386(1)(1 page Abstract only) (1975).

Brownlee, M. et al., "A Glucose–Controlled Insulin–Delivery System: Semisynthetic Insulin Bound to Lectin", *Science*, 206(4423):1190–1191 (Dec. 7, 1979).

Cass, A.E.G. et al., "Ferricinum Ion As An Electron Acceptor for Oxido–Reductases," *J. Electroanal. Chem.*, 190:117–127 (1985).

Cass, A.E.G. et al., "Ferrocene–Mediated Enzyme Electrode for Amperometric Determination of Glucose", *Anal. Chem.*, 56(4):667–671 (Apr. 1984).

Castner, J. F. et al., "Mass Transport and Reaction Kinetic Parameters Determined Electrochemically for Immobilized Glucose Oxidase," *Biochemisty*, 23(10):2203–2210 (1984).

Claremont, D.J. et al., "Biosensors for Continuous In Vivo Glucose Monitoring", *IEEE Engineering in Medicine and Biology Society 10th Annual International Conference*, New Orleans, Louisiana, 3 pgs. (Nov. 4–7, 1988).

Clark, L.C. et al., "Differential Anodic Enzyme Polarography for the Measurement of Glucose", *Oxygen Transport to Tissue: Instrumentation, Methods, and Physiology*, 127–132 (1973).

Clark, L.C., Jr. et al., "Electrode Systems for Continuous Monitoring in Cardiovascular Surgery," *Annals New York Academy of Sciences*, pp. 29–45 (1962).

Clark, L.C. et al., "Long–term Stability of Electroenzymatic Glucose Sensors Implanted in Mice," *Trans. Am. Soc. Artif. Intern. Organs*, XXXIV:259–265 (1988).

Clarke, W. L., et al., "Evaluating Clinical Accuracy of Systems for Self–Monitoring of Blood Glucose," *Diabetes Care*, 10(5):622–628 (Sep.–Oct. 1987).

Csöregi, E. et al., "Design, Characterization, and One–Point in Vivo Calibration of a Subcutaneously Implanted Glucose Electrode," *Anal. Chem.* 66(19):3131–3138 (Oct. 1, 1994).

Csöregi, E. et al., "Design and Optimization of a Selective Subcutaneously Implantable Glucose Electrode Based on "Wired" Glucose Oxidase," *Anal. Chem.* 67(7):1240–1244 (Apr. 1, 1995).

Csöregi, E. et al., "On–Line Glucose Monitoring by Using Microdialysis Sampling and Amperometric Detection Based on "Wired" Glucose Oxidase in Carbon Paste," *Mikrochim. Acta*. 121:31–40 (1995).

Davis, G., "Electrochemical Techniques for the Development of Amperometric Biosensors", *Biosensors*, 1:161–178 (1985).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 1. Electron Transfer from Glucose Oxidase to Metal Electrodes via Electron Relays, Bound Covalently to the Enzyme," *J. Phys. Chem.*, 91(6):1285–1289 (1987).

Degani, Y. et al., "Direct Electrical Communication between Chemically Modified Enzymes and Metal Electrodes. 2. Methods for Bonding Electron–Transfer Relays to Glucose Oxidase and D–Amino–Acid Oxidase," *J. Am. Chem. Soc.*, 110(8):2615–2620 (1988).

Degani, Y. et al., "Electrical Communication between Redox Centers of Glucose Oxidase and Electrodes via Electrostatically and Covalently Bound Redox Polymers," *J. Am. Chem. Soc.*, 111:2357–2358 (1989).

Denisevich, P. et al., "Unidirectional Current Flow and Charge State Trapping at Redox Polymer Interfaces on Bilayer Electrodes: Principles, Experimental Demonstration, and Theory," *J. Am. Chem. Soc.*, 103(16):4727–4737 (1981).

Dicks, J. M., "Ferrocene modified polypyrrole with immobilised glucose oxidase and its application in amperometric glucose microbiosensors," *Ann. Biol. clin.*, 47:607–619 (1989).

Engstrom, R.C., "Electrochemical Pretreatment of Glassy Carbon Electrodes", *Anal. Chem.*, 54(13):2310–2314 (Nov. 1982).

Engstrom, R.C. et al., "Characterization of Electrochemically Pretreated Glassy Carbon Electrodes", *Anal. Chem.*, 56(2):136–141 (Feb. 1984).

Ellis, C. D., "Selectivity and Directed Charge Transfer through an Electroactive Metallopolymer Film," *J. Am. Chem. Soc.*, 103(25):7480–7483 (1981).

Feldman, B.J. et al., "Electron Transfer Kinetics at Redox Polymer/Solution Interfaces Using Microelectrodes and Twin Electrode Thin Layer Cells", *J. Electroanal. Chem.*, 194(1):63–81 (Oct. 10, 1985).

Fischer, H. et al., "Intramolecular Electron Transfer Mediated by 4,4'–Bipyridine and Related Bridging Groups", *J. Am. Chem. Soc.*, 98(18):5512–5517 (Sep. 1, 1976).

Foulds, N.C. et al., "Enzyme Entrapment in Electrically Conducting Polymers," *J. Chem. Soc., Faraday Trans 1.*, 82:1259–1264 (1986).

Foulds, N.C. et al., "Immobilization of Glucose Oxidase in Ferrocene–Modified Pyrrole Polymers," *Anal. Chem.*, 60(22):2473–2478 (Nov. 15, 1988).

Frew, J.E. et al., "Electron–Transfer Biosensors", *Phil. Trans. R. Soc. Lond.*, B316:95–106 (1987).

Gorton, L. et al., "Selective detection in flow analysis based on the combination of immobilized enzymes and chemically modified electrodes," *Analytica Chimica Acta.*, 250:203–248 (1991).

Gregg, B. A. et al., "Cross–Linked Redox Gels Containing Glucose Oxidase for Amperometric Biosensor Applications," *Analytical Chemistry*, 62(3):258–263 (Feb. 1, 1990).

Gregg, B. A. et al., "Redox Polymer Films Containing Enzymes. 1. A Redox–Conducting Epoxy Cement: Synthesis, Characterization, and Electrocatalytic Oxidation of Hydroquinone," *J. Phys. Chem.*, 95(15):5970–5975 (1991).

Hale, P.D. et al., "A New Class of Amperometric Biosensor Incorporating a Polymeric Electron–Transfer Mediator," *J. Am. Chem. Soc.*, 111(9):3482–3484 (1989).

Harrison, D.J. et al., "Characterization of Perfluorosulfonic Acid Polymer Coated Enzyme Electrodes and a Miniaturized Integrated Potentiostat for Glucose Analysis in Whole Blood", *Anal. Chem.*, 60(19):2002–2007 (Oct. 1, 1988).

Hawkridge, F. M. et al., "Indirect Coulometric Titration of Biological Electron Transport Components," *Analytical Chemistry*, 45(7):1021–1027 (Jun. 1973).

Heller, A., "Amperometric biosensors based on three–dimensional hydrogel–forming epoxy networks," *Sensors and Actuators B*, 13–14:180–183 (1993).

Heller, A., "Electrical Connection of Enzyme Redox Centers to Electrodes," *J. Phys. Chem.*, 96(9):3579–3587 (1992).

Heller, A., "Electrical Wiring of Redox Enzymes," *Acc. Chem. Res.*, 23(5):129–134 (1990).

Ianniello, R.M. et al. "Immobilized Enzyme Chemically Modified Electrode as an Amperometric Sensor", *Anal. Chem.*, 53(13):2090–2095 (Nov. 1981).

Ianniello, R.M. et al., "Differential Pulse Voltammetric Study of Direct Electron Transfer in Glucose Oxidase Chemically Modified Graphite Electrodes", *Anal. Chem.*, 54:(7):1098–1101 (Jun. 1981).

Ikeda, T. et al., "Glucose oxidase–immobilized benzoquinone–carbon paste electrode as a glucose sensor," *Agric. Biol. Chem.*, 49(2) (1 page–Abstract only)(1985).

Ikeda, T. et al., "Kinetics of Outer–Sphere Electron Transfers Between Metal Complexes in Solutions and Polymeric Films on Modified Electrodes", *J. Am. Chem. Soc.*, 103(25):7422–7425 (Dec. 16, 1981).

Johnson, J. M. et al., "Potential–Dependent Enzymatic Activity in an Enzyme Thin–Layer Cell," *Anal. Chem.* 54:1377–1383 (1982).

Johnson, K.W., "Reproducible Electrodeposition of Biomolecules for the Fabrication of Miniature Electroenzymatic Biosensors," *Sensors and Actuators B Chemical*, B5:85–89 (1991).

Jönsson, G. et al., "An Amperometric Glucose Sensor Made by Modification of a Graphite Electrode Surface With Immobilized Glucose Oxidase and Adsorbed Mediator", *Biosensors*, 1:355–368 (1985).

Josowicz, M. et al., "Electrochemical Pretreatment of Thin Film Platinum Electrodes", *J. Elecrochem. Soc.*, 135(1):112–115 (Jan. 1988).

Katakis, I. et al., "Electrostatic Control of the Electron Transfer Enabling Binding of Recombinant Glucose Oxidase and Redox Polyelectrolytes," *J. Am. Chem. Soc.*, 116(8):3617–3618 (1994).

Katakis, I. et al., "L–α–Glycerophosphate and L–Lactate Electrodes Based on the Electrochemical "Wiring" of Oxidases," *Analytical Chemisry*, 64(9):1008–1013 (May 1, 1992).

Kenausis, G. et al., "'Wiring' of glucose oxidase and lactate oxidase within a hydrogel made with poly(vinyl pyridine) complexed with $[Os(4,4'\text{–dimethoxy–2,2'–bipyridine})_2 Cl]^{+/2+}$," *J. Chem. Soc., Faraday Trans.*, 92(20):4131–4136 (1996).

Koudelka, M. et al., "In–Vivo Behaviour of Hypodermically Implanted Microfabricated Glucose Sensors", *Biosensors & Bioelectronics*, 6(1):31–36 (1991).

Kulys, J. et al., "Mediatorless peroxidase electrode and preparation of bienzyme sensors," *Bioelectrochemisty and Bioenergetics*, 24:305–311 (1990).

Lager, W. et al., "Implantable Electrocatalytic Glucose Sensor," *Horm. Metab. Res.*, 26:526–530 (Nov. 1994).

Lindner, E. et al. "Flexible (Kapton–Based) Microsensor Arrays of High Stability for Cardiovascular Applications", *J. Chem. Soc.Faraday Trans.*, 89(2):361–367 (Jan. 21, 1993).

Maidan, R. et al., "Elimination of Electrooxidizable Interferant–Produced Currents in Amperometric Biosensors," *Analytical Chemistry*, 64(23):2889–2896 (Dec. 1, 1992).

Mastrototaro, J.J. et al., "An Electroenzymatic Glucose Sensor Fabricated on a Flexible Substrate", *Sensors and Biosensors B Chemical*, B5:139–144 (1991).

McNeil, C. J. et al., "Thermostable Reduced Nicotinamide Adenine Dinucleotide Oxidase: Application to Amperometric Enzyme Assay," *Anal. Chem.*, 61(1):25–29 (Jan. 1, 1989).

Miyawaki, O. et al., "Electrochemical and Glucose Oxidase Coenzyme Activity of Flavin Adenine Dinucleotide Covalently Attached to Glassy Carbon at the Adenine Amino Group", *Biochimica et Biophysica Acta*, 838:60–68 (1985).

Moatti–Sirat, D. et al., "Evaluating in vitro and in vivo the inteference of ascorbate and acetaminophen on glucose detection by a needle–type glucose sensor," *Biosensors & Bioelectronics*, 7(5):345–352 (1992).

Moatti–Sirat, D. et al., "Reduction of acetaminophen interference in glucose sensors by a composite Nafion membrane: demonstration in rats and man," *Diabetologia*, 37(6) (1 page–Abstract only) (Jun. 1994).

Moatti–Sirat, D. et al., "Towards continuous glucose monitoring: in vivo evaluation of a miniaturized glucose sensor implanted for several days in rat subcutaneous tissue," *Diabetologia*, 35(3) (1 page–Abstract only) (Mar. 1992).

Nagy, G. et al., "A New Type of Enzyme Electrode: The Ascorbic Acid Eliminator Electrode," *Life Sciences*, 31(23):2611–2616 (1982).

Nakamura, S. et al., "Effect of Periodate Oxidation on the Structure and Properties of Glucose Oxidase," *Biochimica et Biophysica Acta.*, 445:294–308 (1976).

Narazimhan, K. et al., "p–Benzoquinone activation of metal oxide electrodes for attachment of enzymes," *Enzyme Microb. Technol.*, 7(6)(1 page–Abstract only)(1985).

Ohara, T. J. et al., "Glucose Electrodes Based on Cross–Linked $[Os(bpy)_2CI]^{+/2+}$ Complexed Poly(1–vinylimadazole) Films," *Analytical Chemistry*, 65(23):3512–3516 (Dec. 1, 1993).

Ohara, T. J., "Osmium Bipyridyl Redox Polymers Used in Enzyme Electrodes," *Platinum Metals Rev.*, 39(2):54–62 (Apr. 1995).

Ohara, T. J. et al., ""'Wired" Enzyme Electrodes for Amperometric Determination of Glucose or Lactate in the Presence of Interfering Substances," *Analytical Chemistry*, 66(15):2451–2457 (Aug. 1, 1994).

Olievier, C. N. et al., "In vivo Measurement of Carbon Dioxide Tension with a Miniature Electrode," *Pflugers Arch.* 373:269–272 (1978).

Paddock, R. et al., "Electrocatalytic reduction of hydrogen peroxide via direct electron transfer from pyrolytic graphite electrodes to irreversibly adsorbed cytochrome c peroxidase," *J. Electroanal. Chem.*, 260:487–494 (1989).

Palleschi, G. et al., "A Study of Interferences in Glucose Measurements in Blood by Hydrogen Peroxide Based Glucose Probes", *Anal. Biochem.*, 159:114–121 (1986).

Pankratov, I. et al., "Sol–gel derived renewable–surface biosensors," *Journal of Electroanalytical Chemistry*, 393:35–41 (1995).

Pathak, C. P. et al., "Rapid Photopolymerization of Immunoprotective Gels in Contact with Cells and Tissue," *J. Am. Chem. Soc.*, 114(21):8311–8312 (1992).

Pickup, J., "Developing glucose sensors for in vivo use," *Tibtech*, 11: 285–289 (Jul. 1993).

Pickup, J. C. et al., "In vivo molecular sensing in diabetes mellitus: an implantable glucose sensor with direct electron transfer," *Diabetologia*, 32(3):213–217 (1989).

Pickup, J. et al., "Potentially–implantable, amperometric glucose sensors with mediated electron transfer: improving the operating stability," *Biosensors*, 4(2) (1 page–Abstract only) (1989).

Pishko, M.V. et al., "Amperometric Glucose Microelectrodes Prepared Through Immobilization of Glucose Oxidase in Redox Hydrogels", *Anal. Chem.*, 63(20):2268–2272 (Oct. 15, 1991).

Poitout, V. et al., "A glucose monitoring system for on line estimation in man of blood glucose concentration using a miniaturized glucose sensor implanted in the subcutaneous tissue and a wearable control unit," *Diabetolgia*, 36(7) (1 page–Abstract only) (Jul. 1993).

Poitout, V. et al., "Calibration in dogs of a subcutaneous miniaturized glucose sensor using a glucose meter for blood glucose determination," *Biosensors & Bioelectronics*, 7:587–592 (1992).

Poitout, V. et al., "In vitro and in vivo evaluation in dogs of a miniaturized glucose sensor," *ASAIO Transactions*, 37(3) (1 page–Abstract only) (Jul.–Sep. 1991).

Pollak, A. et al., "Enzyme Immobilization by Condensation Copolymerization into Cross–Linked Polyacrylamide Gels," *J. Am. Chem. Soc.*, 102(20):6324–6336 (1980).

Reach, G. et al., "Can Continuous Glucose Monitoring Be Used for the Treatment of Diabetes?" *Analytical Chemistry*, 64(6):381–386 (Mar. 15, 1992).

Rebrin, K. et al., "Automated Feedback Control of Subcutaneous Glucose Concentration in Diabetic Dogs", *Diabetologia*, 32(8):573–576 (Aug. 1989).

Sakakida, M. et al., "Ferrocene–mediate needle–type glucose sensor covered with newly designed biocompatible membrane," *Sensors and Actuators B*, 13–14:319–322 (1993).

Samuels, G. J. et al., "An Electrode–Supported Oxidation Catalyst Based on Ruthenium (IV). pH "Encapsulation" in a Polymer Film," *J. Am. Chem. Soc.*, 103(2):307–312 (1981).

Sasso, S.V. et al., "Electropolymerized 1,2–Diaminobenzene as a Means to Prevent Interferences and Fouling and to Stabilize Immobilized Enzyme in Electrochemical Biosensors", *Anal. Chem.*, 62(11):1111–1117 (Jun. 1, 1990).

Scheller, F. et al., "Enzyme electrodes and their application," *Phil. Trans. R. Soc, Lond.*, B 316:85–94 (1987).

Schmehl, R.H. et al., "The Effect of Redox Site Concentration on the Rate of Mediated Oxidation of Solution Substrates by a Redox Copolymer Film", *J. Electroanal. Chem.*, 152:97–109 (Aug. 25, 1983).

Shichiri, M. et al., "Glycaemic Control in Pancreatetomized Dogs with a Wearable Artificial Endocrine Pancreas", *Diabetologia*, 24(3):179–184 (Mar. 1983).

Sittampalam, G. et al., "Surface–Modified Electrochemical Detector for Liquid Chromatography", *Anal. Chem.*, 55(9):1608–1610 (Aug. 1983).

Soegijoko, S. et al., *Horm. Metabl. Res., Suppl. Ser*, 12 (1 page–Abstract only) (1982).

Sprules, S. D. et al., "Evaluation of a New Disposable Screen–Printed Sensor Strip for the Measurement of NADH and Its Modification to Produce a Lactate Biosensor Employing Microliter Volumes," *Electroanalysis*, 8(6):539–543 (1996).

Sternberg, F. et al., "Calibration Problems of Subcutaneous Glucosensors when Applied "In–Situ" in Man," *Horm. metabl. Res*, 26:524–525 (1994).

Sternberg, R. et al., "Covalent Enzyme Coupling on Cellulose Acetate Membranes for Glucose Sensor Development," *Analytical Chemistry*, 60(24):2781–2786 (Dec. 15, 1988).

Sternberg, R. et al., "Study and Development of Multilayer Needle–type Enzyme–based Glucose Microsensors," *Biosensors*, 4:27–40 (1988).

Suekane, M., "Immobolization of glucose isomerase," *Zeitschrift für Allgemeine Mikrobiologie*, 22(8):565–576 (1982).

Tajima, S. et al., "Simultaneous Determination of Glucose and 1,5–Anydroglucitol", *Chemical Abstracts*, 111(25):394 111:228556g (Dec. 18, 1989).

Tarasevich, M.R. "Bioelectrocatalysis", *Comprehensive Treatise of Electrochemistry*, 10(Ch. 4):231–295 (1985).

Tatsuma, T. et al., "Enzyme Monolayer– and Bilayer–Modified Tin Oxide Electrodes for the Determination of Hydrogen Peroxide and Glucose," *Anal. Chem.*, 61(21):2352–2355 (Nov. 1, 1989).

Taylor, C. et al., "'Wiring' of glucose oxidase within a hydrogel made with polyvinyl imidazole complexed with $[(Os–4,4'–dimethoxy–2,2'–bipyridine)Cl]^{+/2+}$," *Journal of Electroanalytical Chemistry*, 396:511–515 (1995).

Trojanowicz, M. et al., "Enzyme Entrapped Polypyrrole Modified Electrode for Flow–Injection Determination of Glucose," *Biosensors & Bioelectronics*, 5:149–156 (1990).

Turner, A.P.F. et al., "Diabetes Mellitus: Biosensors for Research and Management", *Biosensors*, 1:85–115 (1985).

Turner, R.F.B. et al., "A Biocompatible Enzyme Electrode for Continuous in vivo Glucose Monitoring in Whole Blood," *Sensors and Actuators*, B1(1–6):561–564 (Jan. 1990).

Tuzhi, P. et al., "Constant Potential Pretreatment of Carbon Fiber Electrodes for In Vivo Electrochemistry", *Analytical Letters*, 24(6):935–945 (1991).

Umaha, M., "Protein–Modified Electrochemically Active Biomaterial Surface," *U.S. Army Research Office Report*, (12 pages) (Dec. 1988).

Urban, G. et al., "Miniaturized Thin–Film Biosensors Using Covalently Immobilized Glucose Oxidase", *Biosensors & Bioelectronics*, 6(7):555–562 (1991).

Velho, G. et al., "In Vitro and In Vivo Stability of Electrode Potentials in Needle–Type Glucose Sensors", *Diabetes*, 38(2):164–171 (Feb. 1989).

Velho, G. et al., "Strategies for calibrating a subcutaneous glucose sensor," *Biomed. Biochin. Acta*, 48(11/12):957–964 (1989).

Von Woedtke, T. et al., "In Situ Calibration of Implanted Electrochemical Glucose Sensors," *Biomed. Biochim. Acta*, 48(11/12):943–952 (1989).

Vreeke, M.S. et al., "Chapter 15: Hydrogen Peroxide Electrodes Based on Electrical Connection of Redox Centers of Various Peroxidases to Electrodes through a Three–Dimensional Electron–Relaying Polymer Network," *Diagnostic Biosensor Polymers*, 7 pgs. (Jul. 26, 1993).

Vreeke, M. et al., "Hydrogen Peroxide and β–Nicotinamide Adenine Dinucleotide Sensing Amperometric Electrodes Based on Electrical Connection of Horseradish Peroxidase Redox Centers to Electrodes through a Three–Dimensional Electron Relaying Polymer Network," *Analytical Chemistry*, 64(24):3084–3090 (Dec. 15, 1992).

Wang, J. et al., "Activation of Glassy Carbon Electrodes by Alternating Current Electrochemical Treatment", *Analytica Chimica Acta*, 167:325–334 (Jan. 1985).

Wang, J. et al., "Amperometric biosensing of organic peroxides with peroxidase–modified electrodes," *Analytica Chimica Acta*. 254:81–88 (1991).

Wang, D. L. et al., "Miniaturized Flexible Amperometric Lactate Probe," *Analytical Chemistry*, 65(8):1069–1073 (Apr. 15, 1993).

Wang, J. et al., "Screen–Printable Sol–Gel Enzyme–Containing Carbon Inks," *Analytical Chemistry*, 68(15):2705–2708 (Aug. 1, 1996).

Wang, J. et al., "Sol–Gel–Derived Metal–Dispersed Carbon Composite Amperometric Biosensors," *Electroanalysis*, 9(1):52–55 (1997).

Williams, D.L. et al., "Electrochemical–Enzymatic Analysis of Blood Glucose and Lactate", *Anal. Chem.*, 42(1):118–121 (Jan. 1970).

Wilson, G. S. et al., "Progress toward the Development of an Implantable Sensor for Glucose," *Clinical Chemistry*, 38(9):1613–1617 (1992).

Yabuki, S. et al., "Electro–conductive Enzyme Membrane," *J. Chem. Soc. Chem. Commun*, 945–946 (1989).

Yang, L. et al., "Determination of Oxidase Enzyme Substrates Using Cross–Flow Thin–Layer Amperometry," *Electroanalysis*, 8(8–9):716–721 (1996).

Yao, S.J. et al., "The Interference of Ascorbate and Urea in Low–Potential Electrochemical Glucose Sensing", *Proceedings of the Twelfth Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 12(2):487–489 (Nov. 1–4, 1990).

Yao, T. et al., "A Chemically–Modified Enzyme Membrane Electrode As An Amperometric Glucose Sensor," *Analytica Chimica Acta.*, 148:27–33 (1983).

Ye, L. et al., "High Current Density "Wired" Quinoprotein Glucose Dehydrogenase Electrode," *Anal. Chem.*, 65(3):238–241 (Feb. 1, 1993).

Yildiz, A. et al., "Evaluation of an Improved Thin–Layer Electrode," *Analytical Chemistry*, 40(70):1018–1024 (Jun. 1968).

Zamzow, K. et al., New Wearable Continuous Blood Glucose Monitor (BGM) and Artificial Pancreas (AP), *Diabetes*, 39:5A(20) (May 1990).

Zhang, Y. et al., "Application of cell culture toxicity tests to the development of implantable biosensors," *Biosensors & Bioelectronics*, 6:653–661 (1991).

Zhang, Y. et al., "Elimination of the Acetaminophen Interference in an Implantable Glucose Sensor," *Anal. Chem.* 66:1183–1188 (1994).

Aisenberg et al., "Blood glucose, level monitoring alarm system," Great Britain Patent GB 1394171, issued May 14, 1975, (Abstract only).

Cerami, "Monitor for continuous in vivo measurement of glucose concentration," United States Patent 4,436,094, issued Mar. 13, 1984, 2 pages (Abstract only).

Franetzki, "Implantable, calibrateable measuring instrument for a body substance and a calibrating method," United States Patent 4,759,371, issued Jul. 26, 1988, 2 pages (Abstract only).

Gilli, "Apparatus and method employing plural electrode configurations for cardioversi on of atrial fibrillation in an arrhythmia control system," United States Patent 5,209,229, issued May 11, 1993, 2 pgs (Abstract only).

Klein, "Control and regulation device for glycemia," Great Britain Patent 1599241A, issued Sep. 30, 1981 (Abstract only).

Klein, "Method and apparatus for the control and regulation of glycemia," United States Patent 4,206,755, issued Jun. 10, 1980, 2 pages (Abstract only).

Lawton, "Implantable electrochemical sensor," United States Patent 4,016,866, issued Apr. 12, 1977, 2 pages (Abstract only).

Vadgama et al., "Sensor devices," United States Patent 5,531,878, issued Jul. 2, 1996, 2 pages (Abstract only).

Abstract from Korf, J. et al., "Monitoring of Glucose and Lactate Using Microdialysis: Applications in Neonates and Rat Brain", *Developmental Neuroscience*, vol. 15, No. 3–5, pp. 240–46 (1993).

Flentge F. et al., "An Enzyne–Reactor for Electrochemical Monitoring of Choline and Acetylcholine: Applications in High–Performance Liquid Chromatography, Brain Tissue, Microdialysis and Cerebrospinal Fluid", *Analytical Biochemistry*, vol. 204, No. 2, pp. 305–310, (Aug. 1, 1992).

Laurell, T., "A Continuous Glucose Monitoring System Based on Microdialysis", *Journal of Med. Eng. & Tech.*, vol. 16, No. 5, pp. 187–193 (Sep./Oct. 1992).

Marko–Varga, G. et al., "Enzyme–Based Biosensor as a Selective Detection Unit in Column Liquid Chromatography", *Journal of Chromatography A*, vol. 660, pp. 153–167 (1994).

Schmidt, F.J. et al., "Calibration of a Wearable Glucose Sensor", *The International Journal of Artificial Organs*, vol. 15, No. 1, pp. 55–61 (1992).